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American Heart Journal

VOL. 53

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Original Communications

THE ROENTGENOLOGIC DIAGNOSIS OF PULMONARY HYPERTENSION IN MITRAL STENOSIS

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THE presence of pulmonary hypertension in mitral stenosis usually is determined by clinical means such as assaying the severity of dyspnea and orthopnea and by the accentuation of the second pulmonic sound. Further indirect evidence is afforded by right ventricular strain or hypertrophy patterns in the electrocardiogram, or by the demonstration of right ventricular enlargement by roentgenography. Direct and quantitative estimation of pulmonary hypertension, however, must be achieved by cardiac catheterization or by direct pressures from the pulmonary artery. These procedures are not generally available, besides being somewhat complicated and hazardous for routine use.

Bearing these latter factors in mind we felt that it would be useful to establish a more readily applicable method to determine the presence or absence of pulmonary hypertension. Such a method is described here, based on correlations between the width of the descending branch of the right pulmonary (hilar) artery in the teleoroentgenogram and the resting mean pulmonary artery pressures measured during cardiac catheterization.

PROCEDURE

The descending branch of the right pulmonary artery lies lateral to the right lower lobe bronchus. The width of the artery is measured in its upper portion at right angles to the bronchus from the bronchus to the outer margin of the vessel (Fig. 1). Comparison of the plain roentgenogram with selective pulmonary angiograms has shown excellent correlation in regard to the accuracy of this method.

Rarely, difficulties are encountered in measuring the width of the vessel. This may occur when a dilated right heart or left atrium projects to the right of and beyond the right lower lobe bronchus. The bronchus must then be looked

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for within the heart shadow (Fig. 2), or, at times, its course can be projected downward as a straight line from its proximal portion at the tracheal bifurcation. Overpenetrated roentgenograms or a slight right anterior oblique projection may bring out the bronchus highlight more clearly.

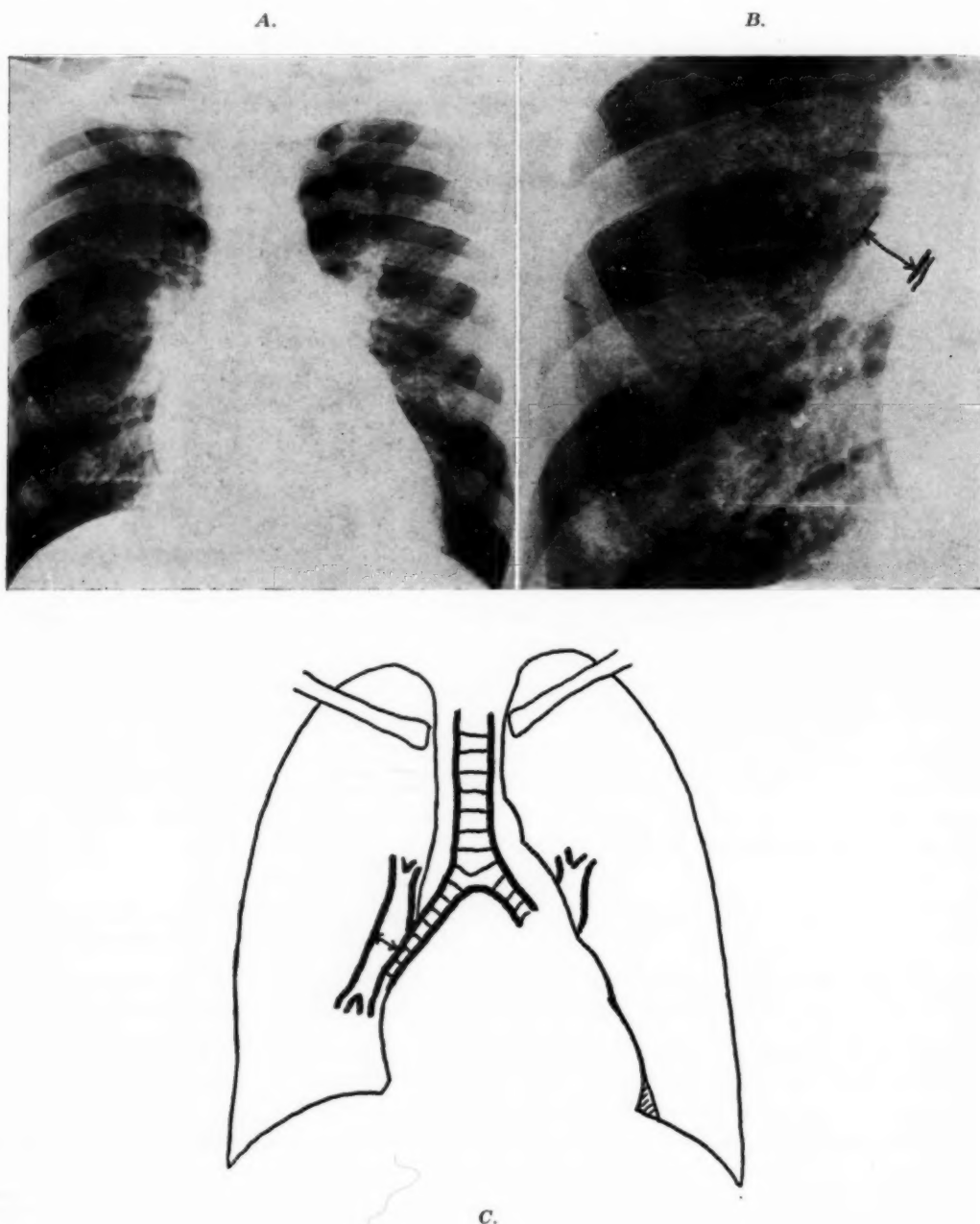


Fig. 1.—A shows the lung fields and the right (hilum) pulmonary artery, along with the cardiac density. B, Magnified view of the right lower lung field illustrating the narrowing of the tertiary pulmonary arterial branches, the diffusely increased pulmonary vascularity, and the method of measuring the width of the descending branch of the right pulmonary artery. C, Diagram of A.

In 6-foot film projections the width of the right descending pulmonary artery branch usually is given as ranging from 9 to 14 mm. To check this the widths of the right descending pulmonary artery were measured in 100 normal hospital employees ranging in age from 18 to 60 years. Ninety per cent of the widths measured from 9 to 13 mm. Only four were 15 mm. or greater; all of these were in the 40 to 60 year age group. Thus the range from 9 to 13 mm. may be considered within normal biologic measurement limits, and measurements exceeding 14 mm. may well be considered abnormal.

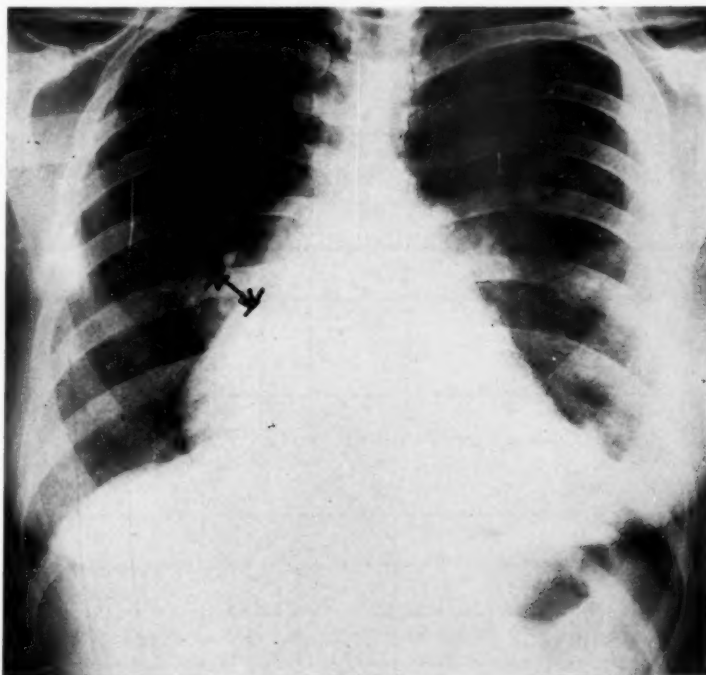
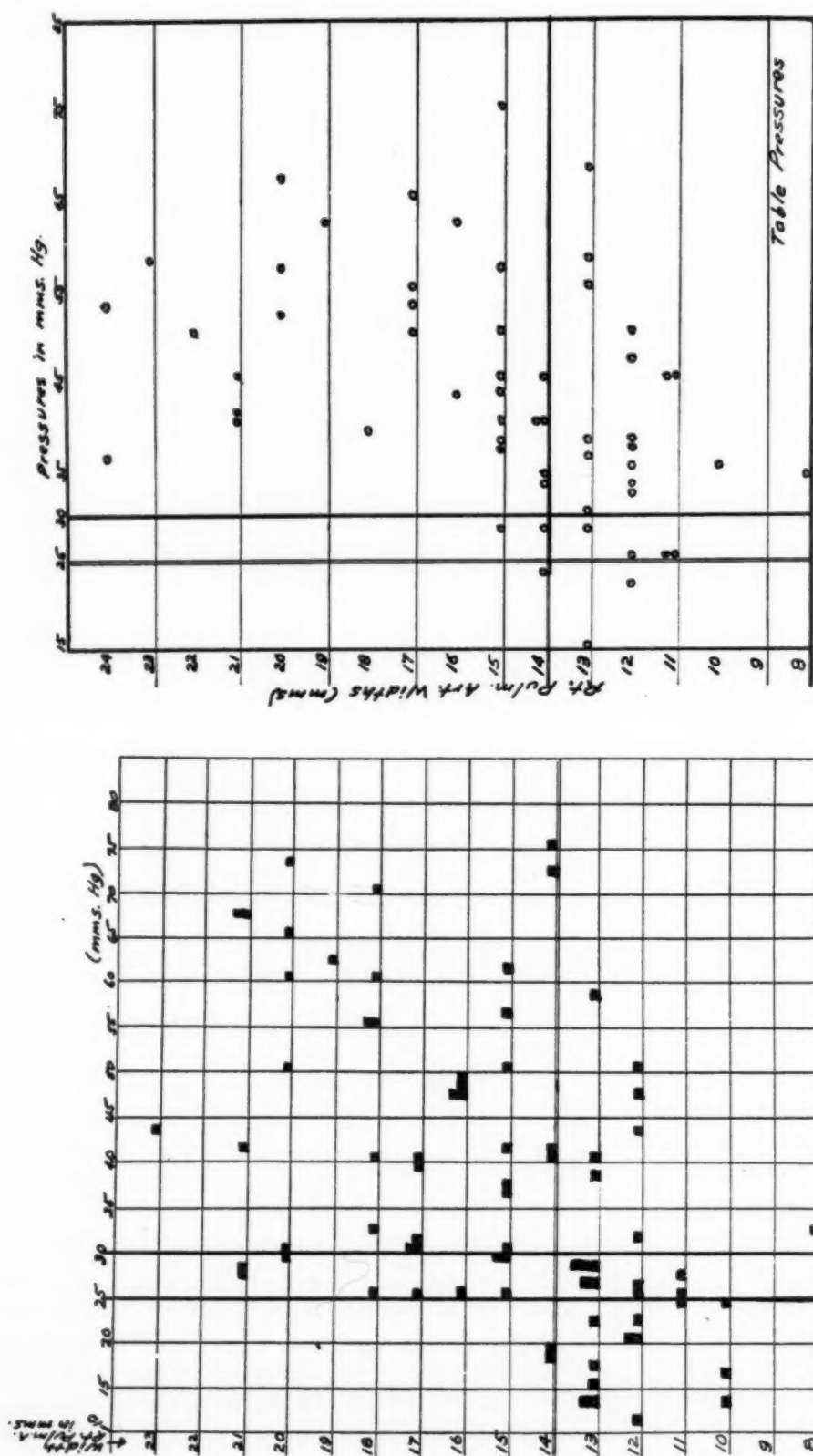


Fig. 2.—The right heart border appears beyond the shadow of the right lower lobe bronchus. The bronchus is barely seen within the heart shadow. Pulmonary artery width 20 mm. Mean pressure 65 mm. Hg.

RESULTS

There were 105 patients with pure or significantly predominant mitral stenosis evaluated in this study. Roentgenograms of two thirds of these were associated with decreased aeration of the lung parenchyma (Fig. 1), and about one fifth showed narrowing of the tertiary pulmonary arteries (Fig. 1), which has been so aptly stressed by Campbell³ and by Davies¹ in England.

Pulmonary artery pressures are available in these 105 patients, 77 by cardiac catheterization, and in 56 as recorded at the time of operation by direct puncture of the pulmonary artery. Fig. 3,4 demonstrates the correlation between the pulmonary artery widths and mean resting pressures during catheterization. The upper limit of normal mean pulmonary artery pressure is regarded as 15 mm. Hg. A mean pressure of 25 mm. or more is considered a significant elevation, and hereafter will be referred to as such. This is 70 per cent above normal.



Of the seventy-seven catheterized patients, forty-seven had right pulmonary artery widths measuring 14 mm. or above (Fig. 3,A). Forty-five of the forty-seven had resting mean pressures exceeding 25 mm. Hg, the other two had less significant elevations. All of the forty-one patients with pulmonary artery widths of 15 mm. or more had significant pressure elevations.

A similar correlation was noted between pulmonary artery widths and pulmonary artery pressures performed at the time of operation by pulmonary artery punctures (Fig. 3,B). Here with pulmonary artery widths of 14 mm. or more, thirty-three of thirty-four patients had pressures of 25 mm. Hg or more. All of the twenty-seven patients with widths of 15 mm. or more showed significant pulmonary artery pressure elevations.

Below 14 mm., pulmonary artery width level correlation is much less reliable. Thirteen of the seventy-seven catheterized patients had neither increased right pulmonary artery width nor significantly increased pulmonary artery pressures. However, seventeen others in this catheterized group showed significant pulmonary hypertension, while their pulmonary artery widths were 13 mm. or less. Therefore, normal pulmonary artery widths might be associated with either normal or elevated pulmonary artery pressures.

DISCUSSION

Others have sought to use the roentgenographic demonstration of the pulmonary artery widening as a reliable objective criterion of pulmonary hypertension. Determination of size has been made grossly rather than by actual measurement. In each study the over-all results have been similar, including occasional cases that are exceptions without adequate explanation.

Dexter's group⁴ demonstrated, in a small series of patients with mitral stenosis, widening of the hilar branches with elevated pulmonary artery pressures. There was no quantitative correlation and it was noted that in one patient there was marked pulmonary artery enlargement with but slightly elevated pressures. Campbell³ roughly correlated the degree of increased width of the right hilar branch with the height of the pulmonary artery pressures.

Davies and his associates,¹ in a careful study of fifty-one patients with mitral stenosis, found the highest grades of pulmonary arterial pressures associated with marked widening of the right hilar branch and the greatest degree of narrowing of the distal (tertiary) branches in the lower lung fields. Here, too, infrequent exceptions occurred. Whitaker,⁵ in a similar study, concluded that extreme prominence of the main branches of the pulmonary artery is indicative of severe pulmonary hypertension and normal branches may be associated with mild hypertension.

There is no direct linear correlation between increased pulmonary artery widths and the degree of pulmonary artery hypertension. A review of the various pressures, resistances, and flows obtained on cardiac catheterization in mitral stenosis fails to yield an adequate explanation for this lack of linear correlation. Most likely the variability is a function of duration of pulmonary hypertension and the intrinsic distensibility and elasticity of the pulmonary vascular system.

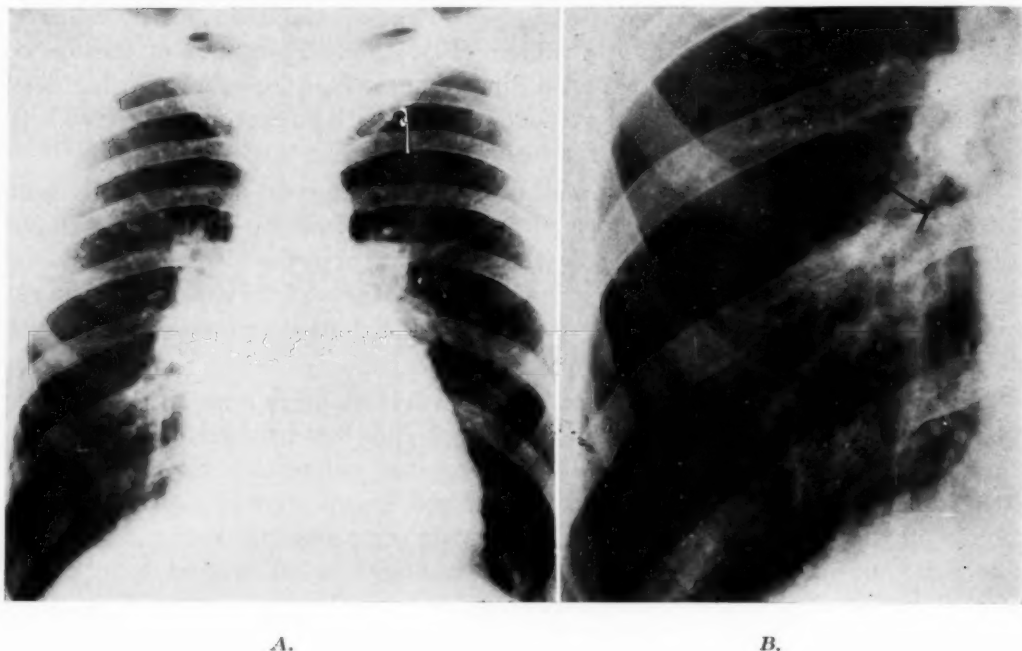


Fig. 4.—*A*, The right hilar branch measures 13 mm. in width, which correlates with the resting mean pulmonary artery pressure of 13 mm. Hg. However, on exercise the pressure rose to 38 mm. Hg. *B*, Magnification of *A* to indicate better the normal width of the pulmonary artery and the normally appearing tertiary branches as compared with Fig. 1, *B*.

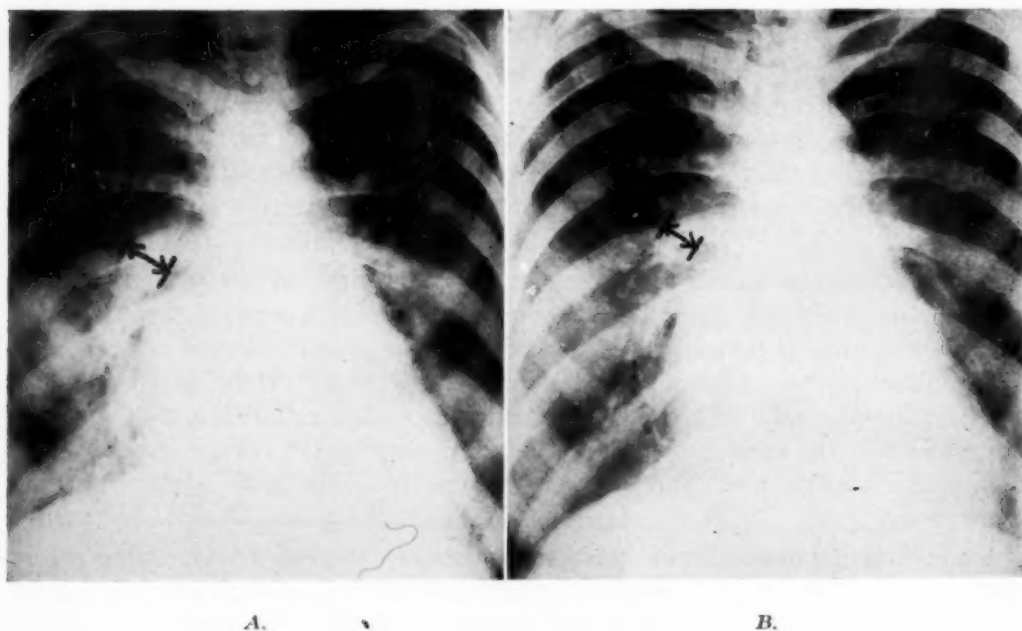


Fig. 5.—*A* illustrates the width of the right hilar branch at time of acute pulmonary edema. *B* demonstrates the decreased size of this vessel on the following day when pulmonary edema had receded.

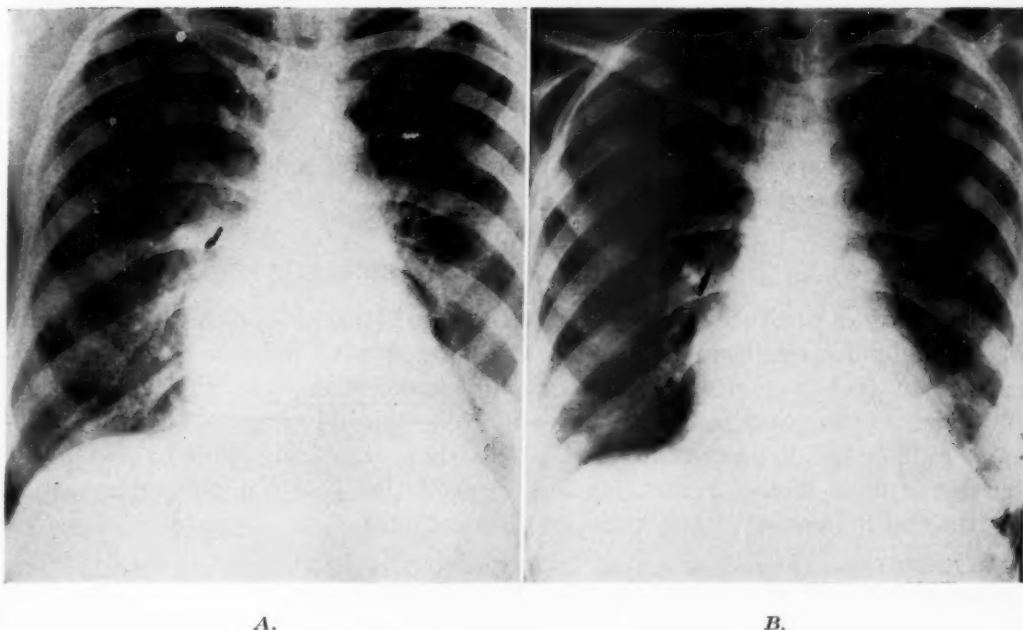


Fig. 6.—Decreased width of the right hilar branch following mitral valvulotomy. *A*, Preoperative. *B*, Fourteen months after the operation. Diminished hilar width.

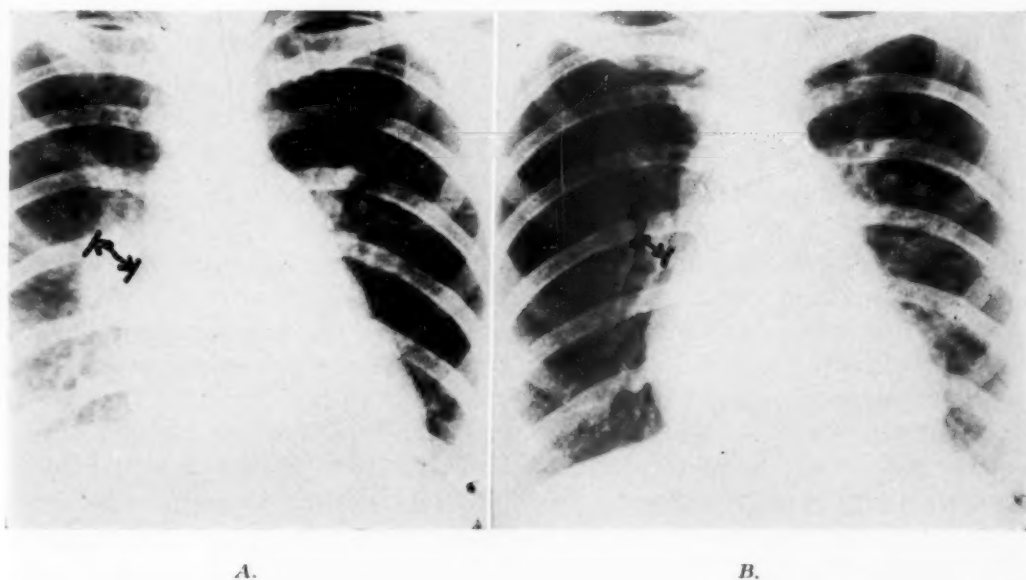


Fig. 7.—Result of mitral valvulotomy. *A* demonstrates a pulmonary artery width of 20 mm. in a patient whose mean pressure was 65 mm. Hg. *B* is the postoperative film taken six months later when the mean pressure was 22 mm. Hg. The right descending pulmonary artery width now measures 12 mm.

Positive and useful conclusions can, however, be drawn. When the right main pulmonary artery branch measures 15 mm. or more in width, pulmonary hypertension of 25 mm. or more is almost surely present. Most likely at this width the pressure will be 30 mm. or higher, i.e., twice the normal value. At 14 mm. widths significant pulmonary hypertension may be present. Below 14 mm. in width there is no certainty as to the existence of pulmonary hypertension as determined by this roentgenographic method.

SUMMARY AND CONCLUSION

A study is presented in patients with mitral stenosis correlating the width of the right descending pulmonary artery branch with pulmonary artery pressures. In such patients roentgenographic demonstration of right descending pulmonary artery widths of 15 mm. or more is definitely associated with significant pulmonary hypertension, and at 14 mm. significant pulmonary hypertension is most likely present. A linear correlation between pulmonary artery widths and pulmonary artery pressure does not exist.

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VARIATIONS IN THE RESPONSE OF NORMAL PERSONS AND CARDIAC PATIENTS TO THE NYLIN HEART FUNCTION TEST

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INDIVIDUALS with organic cardiac disease metabolize a larger amount of oxygen in performing an amount of physical work than do normal persons. A disproportionate increase in oxygen consumption occurs during the period immediately following the cessation of work, resulting in a slower than normal return to the initial rate of oxygen consumption. Measurement of this oxygen debt following standardized work has been utilized as an objective measurement of cardiac functional capacity by Nylin,¹ by Katz and associates,² and others.^{3,4,5} The Nylin staircase test has found broad acceptance due to the ease of walking stairs as a standardized work and, especially in Scandinavia, a large amount of clinical investigation stands behind this test. Utilization of the test at Cook County Hospital has brought forward a greater variation in the response of human beings to the procedure than was generally recognized. Accordingly an investigation was undertaken of the reliability and variability of the test in reference to standards published by Nylin.

PROCEDURE

The function test was performed according to the criteria of Nylin. A standard staircase 1 M. high, having six steps, was employed in such a fashion that the individual being examined walked up and down it in a circular fashion. The low-output test, walking five rounds (climbing up and down the 1 M. staircase ten times) at a rate of 85 steps per minute, and the middle-output test, walking five rounds at 160 steps per minute, were analyzed. Oxygen consumption was determined at rest and then between the second and fifth minute after the cessation of the work. A Benedict-Roth type machine, manufactured by The Sanborn Company, was employed. The increase in oxygen consumption after cessation of work was calculated as a percentage of the resting values.

Two methods of analysis were employed. Single tests were first performed on a group of individuals with normal cardiovascular systems. Eighteen normal men, mean age 37.3 years, performed the 5/85 test, while fourteen normal men,

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mean age 32.4 years, performed the 5/160 test. The minimum, maximum, and mean increases in oxygen consumption were obtained, and the standard deviation and error were calculated for the mean.

Secondly the consistency of the tests in a single person was examined. In a group of twelve normal individuals and persons with cardiac disease, stable by all other criteria, the 5/85 test was performed two or three times at intervals of a few days by each individual for a total of 31 tests. The 5/160 test was also done at least twice by each of a group of six persons, a total of 16 tests. In this case the minimum, maximum, and mean variations observed in the respective individuals were obtained.

RESULTS AND DISCUSSION

The results are summarized in Tables I and II. In single tests performed by normal men the per cent of increase in oxygen consumption after the 5/85 test ranged from 0 to 59 per cent (mean = 29, S. D. = ± 17), after the 5/160 test they ranged from 15 to 89 per cent (mean = 55, S. D. = ± 26.9). The mean figures are remarkably similar to those arrived at by Nylin many years ago and which are still employed by him, mainly; the highest normal value for the relative O_2 debit for the 5/85 test was 30 per cent, for the 5/160 test was 75 per cent. It deserves emphasis that this range for normal persons is much greater than that published by North American observers (Sutton, F. C.⁴: 5/80 test—mean = 19 per cent and 5/160 test—mean = 30 per cent; also Sodeman³: 100-step rate = + 31 per cent, 200-step rate = + 41 per cent). The statistical analysis of the present figures illustrates the great range of normalcy and contributes the first such analysis presented. Knowledge of the standard deviation and error of the mean were essential to compare groups of individuals on whom the tests were performed. The unpublished statistical values employed by Nylin for the 5/80 test are: $\epsilon(M) = 3.47$.⁶

TABLE I. RANGE IN THE RESPONSE OF NORMAL MALE INDIVIDUALS TO THE NYLIN HEART FUNCTION TEST. RESULTS OF SINGLE TESTS PERFORMED ON A GROUP OF INDIVIDUALS

GROUP OF INDIVIDUALS			RELATIVE OXYGEN DEBT IN PER CENT				
Test	Number of Individuals	Mean Age (Years)	Min.	Max.	Mean	S. D.	$\epsilon(M)$
10/80	18	37.3	0	59	29	± 17	± 4.1
10/160	14	32.4	15	89	55	± 26.9	± 7.8

While the above illustrated the range within which comparison of group response to the oxygen debt test will be found, no other figures were available for the reliability of the test in a single individual. In the course of other experiments it was found that individual responses were widely variable. As seen in Table II, the oxygen debt seen in one individual in the same clinical status subjected to repeated daily testing varied day by day by as little as 2 per cent and by as much as 53 per cent. For the group of eighteen studies the results of daily

TABLE II. VARIATION IN THE RESPONSE OF NORMAL PERSONS AND CARDIAC INVALIDS REPEATEDLY SUBJECTED TO THE NYLIN HEART FUNCTION TEST. RESULTS OF REPEATED DAILY TESTING OF A GROUP OF INDIVIDUALS

GROUP OF INDIVIDUALS				VARIATION IN RELATIVE OXYGEN DEBT			
Test	Number of Individuals	Mean Age (Years)	No. of Tests Performed	Min.	Max.	Mean	S. D.
10/80	12	53.8	31	2	52	25.6	15.3
10/160	6	37.3	16	5	53	28	22.1

tests differed in the mean individual by about 26 per cent increase in oxygen debt for both the 10/80 and 10/160 tests. This variation in individual response to the test was so great that the procedure lost value as a method of following the course of any single cardiac patient. This spontaneous variation may be due to the fact that the cardiac patient is so limited by his dyspnea, to a varying degree, that insufficient and different amounts of muscular activity can be done without causing the same amount of oxygen debt. It should be added that, among the older patients, the daily variation in the test was greater than among the younger.

Within these limits the oxygen debt cardiac function test has value in the objective comparison of groups of individuals, but has not proved reliable in following the course of individual cardiac patients. This limitation must be added to these previously recognized and outlined by Sodeman³: the test is slow and time consuming; overlapping between normal persons and patients with heart disease is considerable; and it is a measure of pulmonary as well as cardiac function.

SUMMARY

1. The Nylin staircase cardiac function test was performed repeatedly on normal individuals and on a group of cardiac patients.
2. Results and statistical characteristics indicate that the mean figures obtained from a group of persons studied had wide variations, but could be satisfactorily compared.
3. The spontaneous daily variation seen in the response of an individual to the test is of such a magnitude that the test was not satisfactory to follow a single individual's cardiac status.

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A METHOD FOR APPLYING APPROXIMATELY IDEAL LEAD CONNECTIONS TO HOMOGENEOUS VOLUME CONDUCTORS OF IRREGULAR SHAPE

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THE introduction of the lead vector¹ and lead field²⁻⁴ concepts into electrocardiographic theory has stimulated considerable interest in the possibility of devising lead connections which will accurately record desired components of the electromotive forces of the heart. Presumably the primary objective of such studies is orthogonalization of the electrocardiographic frame of reference. Such orthogonalization would permit the accurate registration of the spatial vectorcardiogram, and holds some promise of simplifying scalar electrocardiography.

By definition, the lead field is the electrical field produced in the body when a lead connection is energized with one unit of electrical current from an external electromotive source. The rate at which the potential of the lead field increases within the body is a vector point function known as the gradient. In a previous publication it was shown that the gradient of the field is identical to the lead vector of the particular lead connection.⁵

In general, lead fields are not uniform in the cardiac region. Therefore the lead vector tends to vary in both magnitude and orientation in this region, and the associated lead connection does not accurately record a given single component of the heart vector. Ideal lead connections may be defined as those whose associated lead fields are uniform in the cardiac region. Because of this uniformity accurate projection of the heart vector on the lead axis may be realized.

By means of cut-and-try methods a number of attempts have been made to devise ideal lead connections.^{4,6,7} In contradistinction to such relatively empiric methods, it is the purpose of this communication to show how approximately ideal lead connections may be applied to irregularly shaped, homogeneous volume conductors on the basis of well-defined theoretical principles.

The fundamental principle of the method is demonstrated in Fig. 1. At the top of the figure an irregularly shaped lamina is shown as immersed in a very long rectangular strip having the same electrical conductivity as the lamina. Under these conditions current applied through the electrodes at the ends of the rectangular strip will result in a perfectly uniform lead field in the lamina.

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In the middle of the figure the portions of the rectangular strip to either side of the lamina are subdivided into five narrower strips of equal width. Application of current through electrodes at the ends of the narrower strips will produce an essentially uniform lead field in the lamina.

Finally, in the bottom of the figure the strips are replaced by equal resistors of relatively large magnitude which are connected to the lamina at the midpoints of the strips. External energization of the lead connection thus formed should produce an approximately uniform lead field within the lamina.

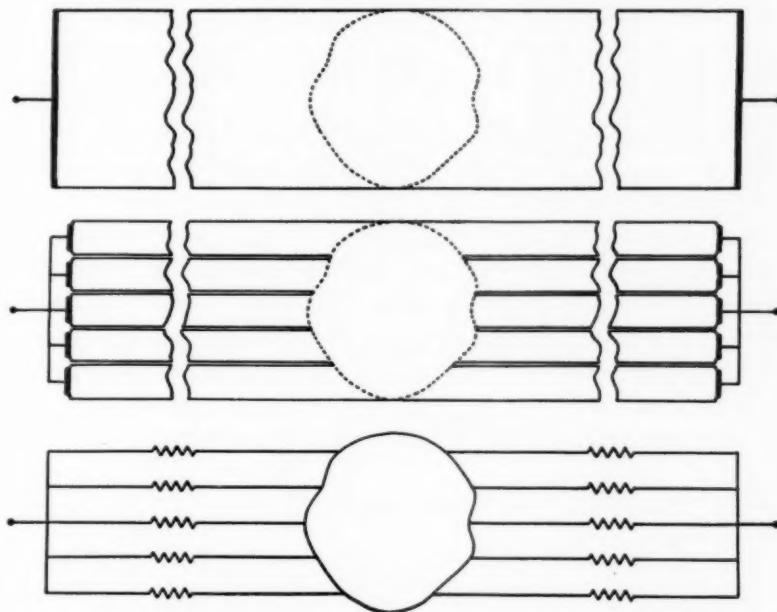


Fig. 1.—Illustration of the principle by which matched resistor networks may be used to form approximately ideal lead connections.

The example shown in Fig. 1 is two dimensional in order to simplify representation. Essentially the same principles apply to the three-dimensional situation in which case a volume conductor is divided into a number of straight parallel tubes of equal cross-sectional area, and equal resistors of relatively large magnitude are connected to the ends of the tubes at their midpoints. It is not mandatory that the tubes be of equal cross-sectional area, but it is desirable that they be so in order that equal resistors may be employed.

Tying the free ends of the resistors together into two terminals similar to those shown in Fig. 1, and then energizing these terminals with 1 milliamperes of current from an external source will produce a lead field current intensity of approximately $1/S_{yz}$ milliamperes per square centimeter, where S_{yz} is the area of the volume conductor surface projected on a plane normal to the lead axis. The magnitude of the associated lead vector is ρ/S_{yz} millivolts per centimeter, where ρ is the specific resistivity of the volume conductor in ohm-centimeters.

Applying Helmholtz's law of reciprocity⁴ to the above results, a current dipole of moment M located within the volume conductor will produce a potential difference of approximately $M_x \rho/S_{yz}$ between the common terminals of the

resistor networks, where M_x is the lead axis component of the dipole moment. Regrouping of the terms gives the relationship

$$M_x = \bar{V} S_{yz}/\rho \text{----- (1),}$$

where \bar{V} is the potential difference between the two resistor terminals, and the bar over this symbol indicates that the surface potential at many points has been averaged by the resistor networks.

As indicated, this relationship is an approximate one. An exact relationship is obtained by dividing the volume conductor into an infinite number of parallel tubes. This yields the expression

$$M_x = \frac{1}{\rho} \int \int_s \mathbf{i} \cdot \mathbf{N} V dS \text{----- (2)}$$

where \mathbf{i} is the unit positive vector parallel to the lead axis, \mathbf{N} is the unit normal vector on the surface of the volume conductor, and V is the potential on the surface of the volume conductor.

The above expression is identical to that which Gabor and Nelson⁸ derived by means of Green's theorem, and the present method of derivation provides confirmation of this phase of their work. Because the hypothetical lead connection which would perform the integration of Equation 2 is truly ideal, the equation applies with equal validity not only to a single dipole but also to the electrical moment produced by myriads of electrical sources and sinks scattered throughout all or part of the volume conductor.

METHODS AND RESULTS

The primary purpose of this study was to determine whether the type of approximation indicated in Fig. 1 might be adequate for eventual clinical application. To test this possibility a number of two-dimensional, electrically homogeneous models were cut out of electrically conducting paper.* Electrodes and resistor networks were applied as indicated by theoretical considerations. The lead connections thus formed were reciprocally energized with 1 milliamperes of direct current and the isopotential lines of the resulting lead fields were mapped at intervals of 150 millivolts of potential difference. A null-reading vacuum tube voltmeter was employed which was sensitive enough to insure precision of the mapping procedure to within 1/100 of an inch or better.

A fine-grained analysis of the results was not attempted since it seemed rather clear from application of a straight edge to various portions of the lead fields which areas were satisfactorily uniform. However, Helm⁹ has described a method for precise analysis which, with suitable modifications, is undoubtedly applicable to studies of the type described here.

In the first phase of the study a number of irregularly shaped laminas were ruled off in strips of equal width parallel to the axis of the desired ideal lead connection, and electrodes were placed on the periphery of the lamina at positions corresponding to the center of each of the strips. All of the electrodes occurring at positions whose boundary normal formed an angle of less than 90 degrees

*Analogue computing paper, Sunshine Scientific Instruments, Philadelphia, Pa.

with the positive direction of the lead axis were connected together through a yoke of equal resistors. The remaining electrodes were connected through a similar yoke. Each resistor had a nominal value of 1 megohm, which was three hundred times or more the resistance between any two electrodes on the model. The resistors were selected so that the components within each yoke matched to within $\pm \frac{1}{4}$ per cent.

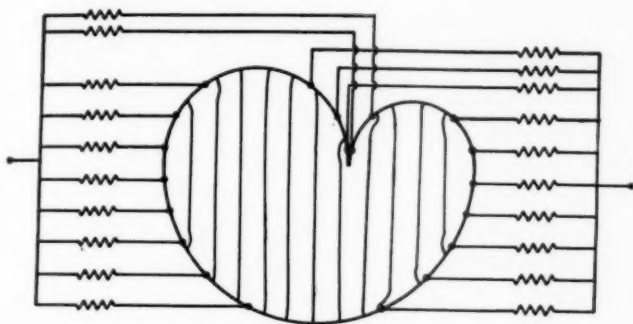


Fig. 2.—Lead field (isopotential distribution) obtained in an irregular laminar model by applying matched ten-resistor arrays according to the principles described in the text and illustrated in Fig. 1.

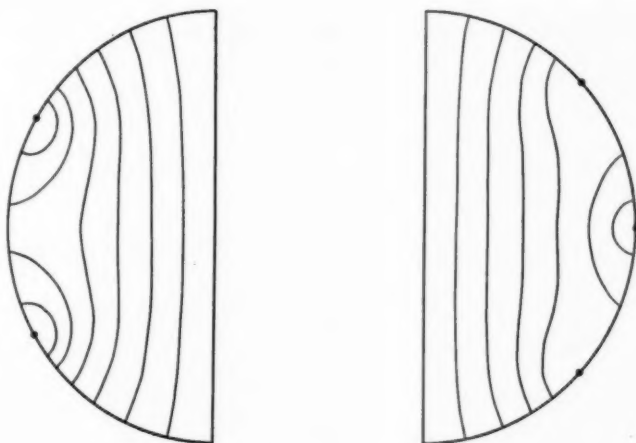


Fig. 3.—Halves of circular models to which balanced resistor networks were applied according to the method described in the text. Two- and three-resistor networks were employed in the left and right sides of the illustration, respectively.

Fig. 2 shows the lead field obtained in such an irregularly shaped lamina 10 inches long and 8 inches wide ruled into eight horizontal strips 1 inch wide. The field appears to be strikingly uniform except near the periphery of the model where the isopotential lines are necessarily normal to the boundary, and especially in the vicinity of the electrodes where the isopotential lines tend to degenerate into circular arcs. With these exceptions, however, the lead array shown in the figure provides an excellent approximation of the theoretically ideal situation. Essentially as good results were obtained for other irregularly shaped laminas when the full set of ten resistors per yoke was employed.

In order to gain some idea of how simple a network is required to obtain a usable approximation, we prepared a series of circular laminas 12 inches in diameter with pairs of two-, three-, four-, six-, and nine-resistor yokes which were connected to point electrodes located on the periphery of the laminas according to the strip method outlined above. The lead fields obtained in these studies are shown in Fig. 3 through 5.

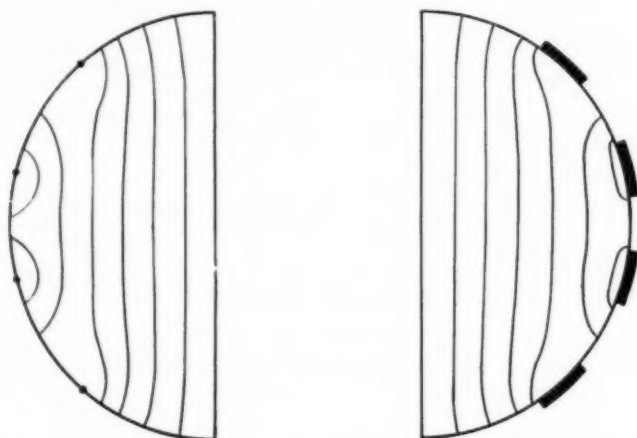


Fig. 4.—Halves of circular models to which balanced four-resistor arrays were applied according to the method described in the text. Point electrodes were employed in the left side of the illustration, and tab electrodes in the right side.

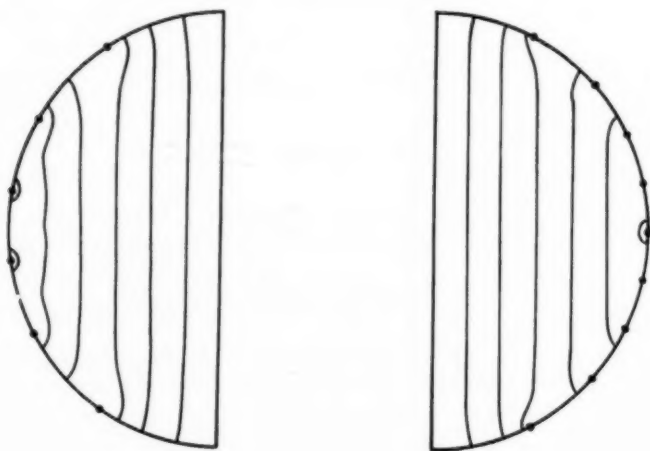


Fig. 5.—Halves of circular models to which balanced resistor networks were applied according to the method described in the text. Six- and nine-resistor networks were employed in the left and right sides of the illustration, respectively.

As anticipated, the excellence of the lead fields was directly related to the number of resistor components employed. The nine-resistor arrays produced the best results, and the two-resistor arrays the poorest. The lead fields obtained with the four-resistor arrays indicated that this particular connection was reasonably accurate for eccentricities within the model of up to 50 per cent. The size

of the electrodes apparently is not critical, as shown in Fig. 4. The left half of the figure shows the lead field obtained when a four-resistor array is connected to point electrodes on the lamina; in the right half of the figure the resistors are connected to electrodes made by painting relatively wide tabs with silver ink.*

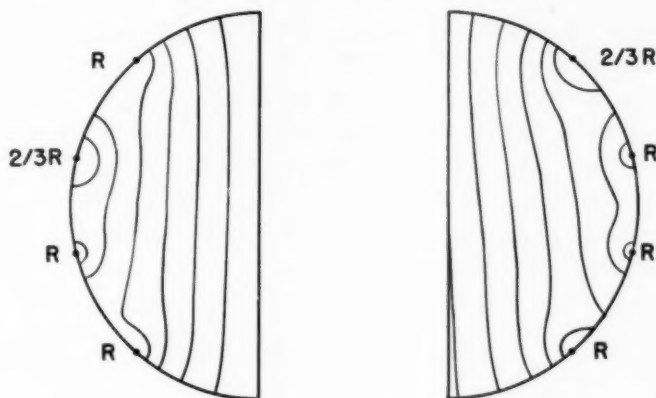


Fig. 6.—Halves of circular models illustrating the distortion of lead fields by unbalanced resistor networks. In both cases four point electrodes were located on each side of the model according to the method described in the text. The resistors connected to each of the electrodes were all of identical value with the single exceptions shown in the illustration. $R = 500,000$ ohms.

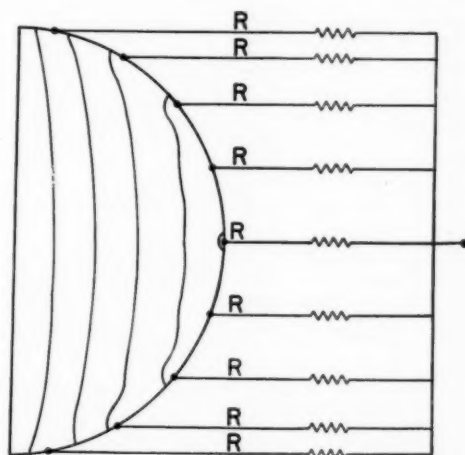


Fig. 7.—Half of a circular model in which matched resistor networks were applied to improperly located electrodes. Each side of the model was divided into equal intervals of boundary arc, with a point electrode located at the middle of each interval. This method of electrode placement is contrary to the equal strip principle described in the text. $R = 1$ megohm.

The lead field obtained with tab electrodes is slightly superior to that obtained with the point electrodes. This is probably due to the fact that reciprocal energization through the tabs more closely resembles the conditions shown in the center of Fig. 1 than does reciprocal energization through point electrodes.

In order to gain some idea of how critically the components of the resistor yokes must be matched we prepared some four-resistor arrays which were de-

*Silver print No. 21-2, General Cement Company.

liberately mismatched, as shown in Fig. 6. Rather surprisingly, a mismatched resistor applied to an electrode near the axis of the lead did not produce severe distortion of the lead field. The same resistor applied to an electrode more remote from the lead axis produced a more serious degree of lead-field distortion, as shown in the right half of Fig. 6. On the basis of these results it seems likely that "gold band" (± 5 per cent) stock resistors would be entirely suitable for clinical applications.

It might be assumed that averaging networks such as used here should be applied to equal subdivisions of the surface area. The incorrectness of this assumption is demonstrated in Fig. 7 where an electrode is located at the mid-point of each 20 degrees of peripheral arc on a circular model. Reciprocal energization of this arrangement through equal resistors produces a lead field which deviates decidedly from the ideal configuration.

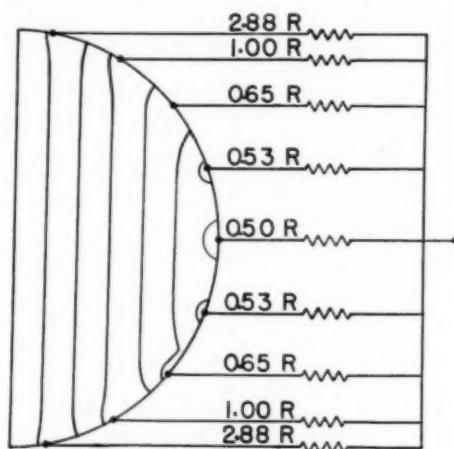


Fig. 8.—The electrode placement is the same as in Fig. 7, but the individual resistors have been weighted according to theoretical considerations described in the text. Proper weighting, as shown here, results in a much more nearly ideal field configuration, but is probably too complicated for clinical application. $R = 1$ megohm.

If one desires to divide the external surface into equal subdivisions it is necessary to give each electrode a weight directly proportional to the product $i \cdot N$ which appears in Equation 2. In our two-dimensional demonstration this was accomplished by making each resistor directly proportional to the secant of the angle between the lead axis and the radius vector of the electrode to which the resistor was connected. Fig. 8 shows that this type of electrode weighting results in a good lead-field configuration and provides further confirmation of the validity of the basic theoretical assumptions.

DISCUSSION

Compounding of electrodes to form leads whose fields are nearly uniform is not a new idea. McFee and Johnston⁴ suggested electrode-resistor combinations for improved registration of lateral and anteroposterior components of the electromotive forces of the heart; and Abildskov and Pence¹⁰ have already applied these suggestions to clinical vectorcardiography. However, these combinations appear

to have been based on lead-field construction according to the method of curvilinear squares,^{2,11} which, in our opinion, does not fully exploit the possibilities for rather strict quantitation. In our study of a two-dimensional model, the possibilities of strict quantitation were exploited rather fully, but we felt we had simply demonstrated a principle rather than having produced numerical values which could be applied without modification to the three-dimensional case.⁶

In this category of compounded leads, the SVEC III⁷ system consists of a set of three lead connections whose vectors are essentially orthogonal and nearly invariant throughout the entire cardiac region of a three-dimensional, electrically homogeneous model.⁷ We feel that this lead system is probably the most accurate of those presently available.

Frank's lead system consists of seven electrodes joined by resistors of proper magnitude.¹² Both the electrode locations and the resistor values are based on an elaborately executed series of experiments on models and humans, and electrode positioning on the individual subject is a relatively simple procedure. In many respects this lead system provides rather accurate registration of the normal QRS forces for clinical purposes. On the other hand, the accuracy of this system for the P, T, and abnormally conducted QRS forces is questionable.

The method of electrode application described here insures "ideal" lead connections because it is derived from incontrovertible physical principles. Therefore it may be applied with a reasonable sense of security to various types of human torsos. In contrast, the SVEC III⁷ and Frank¹² lead systems are derived from experiments performed on a necessarily limited number of three dimensional phantoms and humans. Until their results are confirmed on a larger number of subjects under a variety of conditions, there must be some hesitancy in accepting their general validity. This is particularly true of Frank's system, partly for the reasons stated above, and partly because of the studies of Nelson and Hecht¹³ which indicate that the heart vector of some subjects is best represented as two or more effective cardiac dipoles.

Despite the meritorious aspects of the lead connections proposed here, they suffer the disadvantage of complexity. For instance, five horizontal banks of four electrodes might have to be applied to both the front and back of the torso in order to record the anteroposterior component of the heart vector adequately. The technical difficulties would multiply as the registration of more components was required.

Nevertheless, the possibility of surmounting these practical difficulties might profitably be explored because such efforts could eventuate in an orthogonalized and normalized frame of reference. The accuracy of this frame of reference in the registration of the electromotive forces of the heart as effective heart vectors would clearly be independent of the locus of origin and propagation pathway of electrical impulses in the heart. It would also be unaffected by any possible multiplicity of equivalent cardiac dipoles.

SUMMARY

1. Approximately ideal lead connections may be applied to irregularly shaped, electrically homogeneous volume conductors on the basis of well-defined theoretical principles rather than by means of trial and error methods.

2. These underlying principles were tested and amply confirmed by studies conducted on a series of laminar models.

3. This study confirms both theoretically and experimentally the relationship that the electrical moment due to a number of sources and sinks within a homogeneous volume conductor is equivalent to a surface integral involving unit normals and surface potentials.

4. The method of ideal lead connection proposed here would undoubtedly be cumbersome, but it might profitably be applied to scalar and vector electrocardiography at an investigative level.

I am indebted to W. E. Romans for a number of valuable suggestions, and to F. C. Allen, Jr., and Mrs. M. C. White for technical assistance.

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FREQUENCY SPECTRA OF SOME NORMAL HEART SOUNDS

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RECENTLY a number of papers have appeared which demonstrate the practical use of sonic spectrography in the analysis of cardiovascular sound.¹⁻⁴ The sound spectrograph in the above-mentioned studies presents three variables of the heart sounds on recording paper. Time is displayed along the abscissa, frequency on the ordinate, and intensity by the degree of blackness of any given portion of the record. When the frequency spectrum of a specific heart sound is required the time variable may be eliminated and the frequency-amplitude relationships displayed on two-dimensional coordinates. The purpose of this paper is to demonstrate the frequency spectra of some selected heart sounds and to describe the method in which they were obtained.

METHOD

The heart sounds were analyzed on a modified commercially available heterodyne-type sonic analyzer which uses oscilloscopic presentation. Frequency is displayed on a linear horizontal scale 100 cycles wide which can be any selected increment between 0 and 20 kilocycles per second. Amplitude is displayed on a logarithmic vertical scale of 40 db. Heart sounds consisting of at least one complete cardiac cycle are recorded on a magnetic tape loop. A trigger pulse is also recorded on the loop near the beginning of the sequence. The selected series of heart sounds are examined and photographed, using conventional oscilloscopic techniques. Suitable timing markers are also included in the phonocardiogram. The results shown in this paper were obtained by cutting out the first and second heart sounds from the sequence loop and splicing each sound into a short blank loop. Each of the two loops then contained only one heart sound. The first heart sound spectrum was obtained from four separate time-exposed photographs, each covering a 100 cycle wide section between 0 and 400 cycles per second. Each exposure of three minutes' duration recorded the cumulative deflections of approximately 180 sweeps of the analyzer. Since the heart sound occurred once during every sweep, and the loop repetition rate was slightly out of phase with the analyzer sweep, the time-exposed photograph shows the spectrum of the heart sound for the selected frequency range. The second heart sound was analyzed in the same manner.

A more practical analysis system is shown in Fig. 1. In this instrument arrangement the sequence of heart sounds are left on the original tape loop. The trigger pulse is used to initiate an adjustable delay interval, trigger the sweep

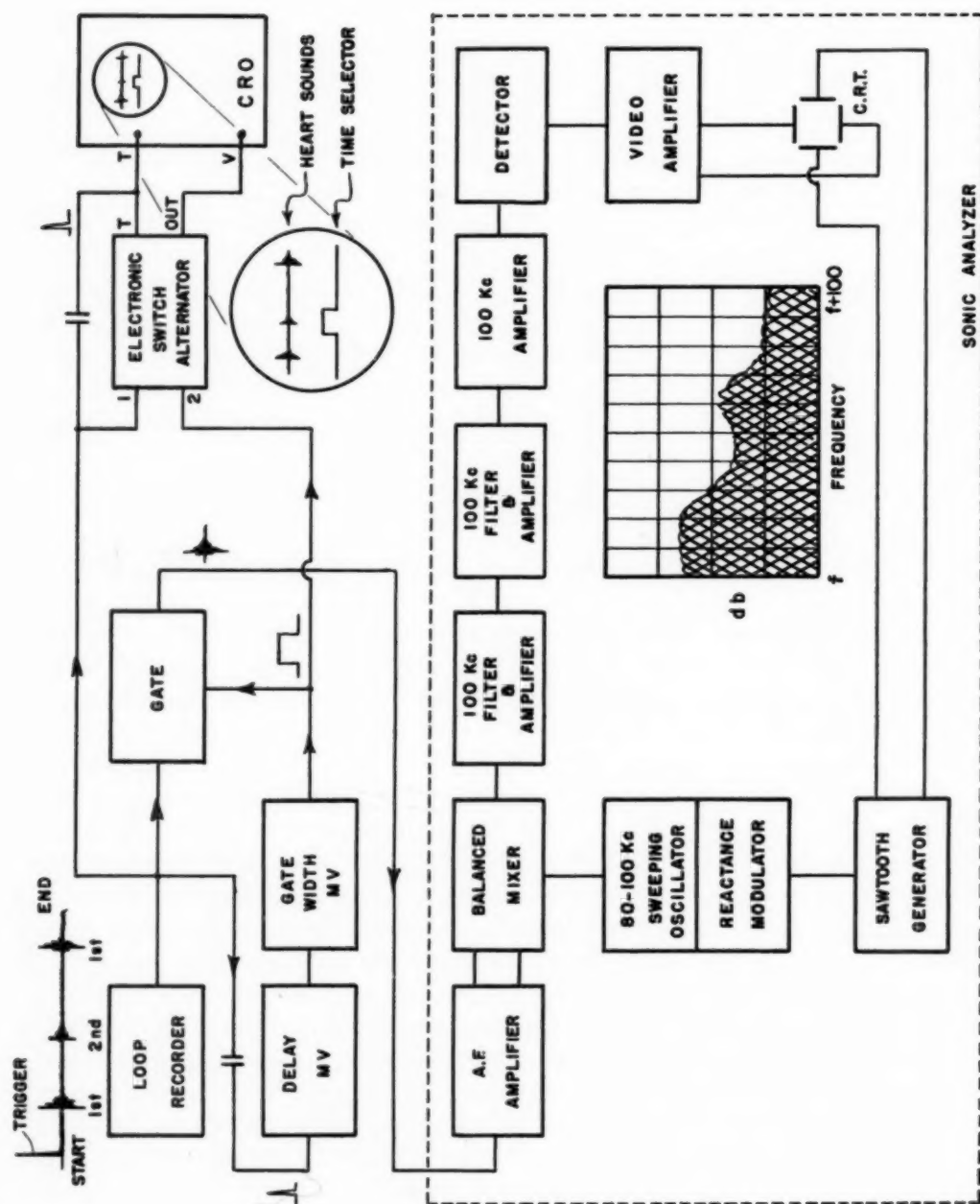


Fig. 1.—Instrument arrangement showing a practical method for obtaining frequency spectra of heart sounds.

of an oscilloscope, and trigger the input selector of an electronic switch alternator. At the termination of the delay interval a time selector pulse opens the gate circuit, thereby allowing the tape recorder output to pass to the sonic analyzer. The gate length multivibrator may be adjusted to provide a suitable gating period. The sequence of heart sounds and the time selector pulse are alternately displayed in their proper time relationship on the oscilloscope. In this manner only a single heart sound is allowed to pass to the analyzer. Other sounds may be selected by adjusting the delay interval.

The time selector pulses drawn beneath the phonocardiograms in this paper are intended to show the segment of the recording which was analyzed. The spectra of the heart sounds are shown over a frequency range from 30 cycles per second to 400 cycles per second. The low frequency range was limited by the frequency response of the magnetic tape.

DISCUSSION

The first heart sound is thought to be produced by the combination of (1) an auricular sound with two components, one muscular and the other valvular, and (2) a ventricular sound in which the principal elements are similarly muscular and valvular. The intensity of the first sound thus depends primarily on the mechanism of closure of the auriculoventricular valves and the auricular and ventricular contractions.

Where the P-R interval is normal, the most important influence is the rate of rise of the intraventricular pressure. The auriculoventricular conduction time, as measured by the P-R interval of the electrocardiogram, is closely related to the intensity of the first sound. Fig. 3 shows the relative intensities of first sounds for a short P-R interval (0.13 second) and for a long P-R interval (0.24 second). The sudden distention of the arteries when blood is ejected from the ventricles is probably also important in the production of the first heart sound.

The second sound is caused by the closure of the semilunar valves and the resulting vibrations set up in the valves, in the walls of the arteries, and in the blood column. The second sound, in comparison with the first sound, is usually of shorter duration, higher in pitch, and louder. The recordings of all the heart sounds used in these studies were made with the stethoscope at the apex position; for this reason almost all of the phonocardiograms show the first sound with greater amplitude than the second sound.

The frequency spectrum of the first heart sound is dependent upon the abruptness of closure of the auriculoventricular valves. The more abrupt the valve closure the more prominent will be the higher frequency components of the spectrum. The same holds true for the semilunar valves in the production of the second heart sound. Since the valve closures are not the only sources of the heart sounds it would be more accurate to say that the frequency spectrum of a particular sound is dependent upon the abruptness of the muscular contraction and the corresponding rate of pressure change.⁵

Figs. 2 and 3 show the frequency spectra of some normal heart sounds. Fig. 3 demonstrates the relative intensities of the first and second sounds with a short P-R interval of 0.13 second (top) and a long P-R interval of 0.24 second (bottom).

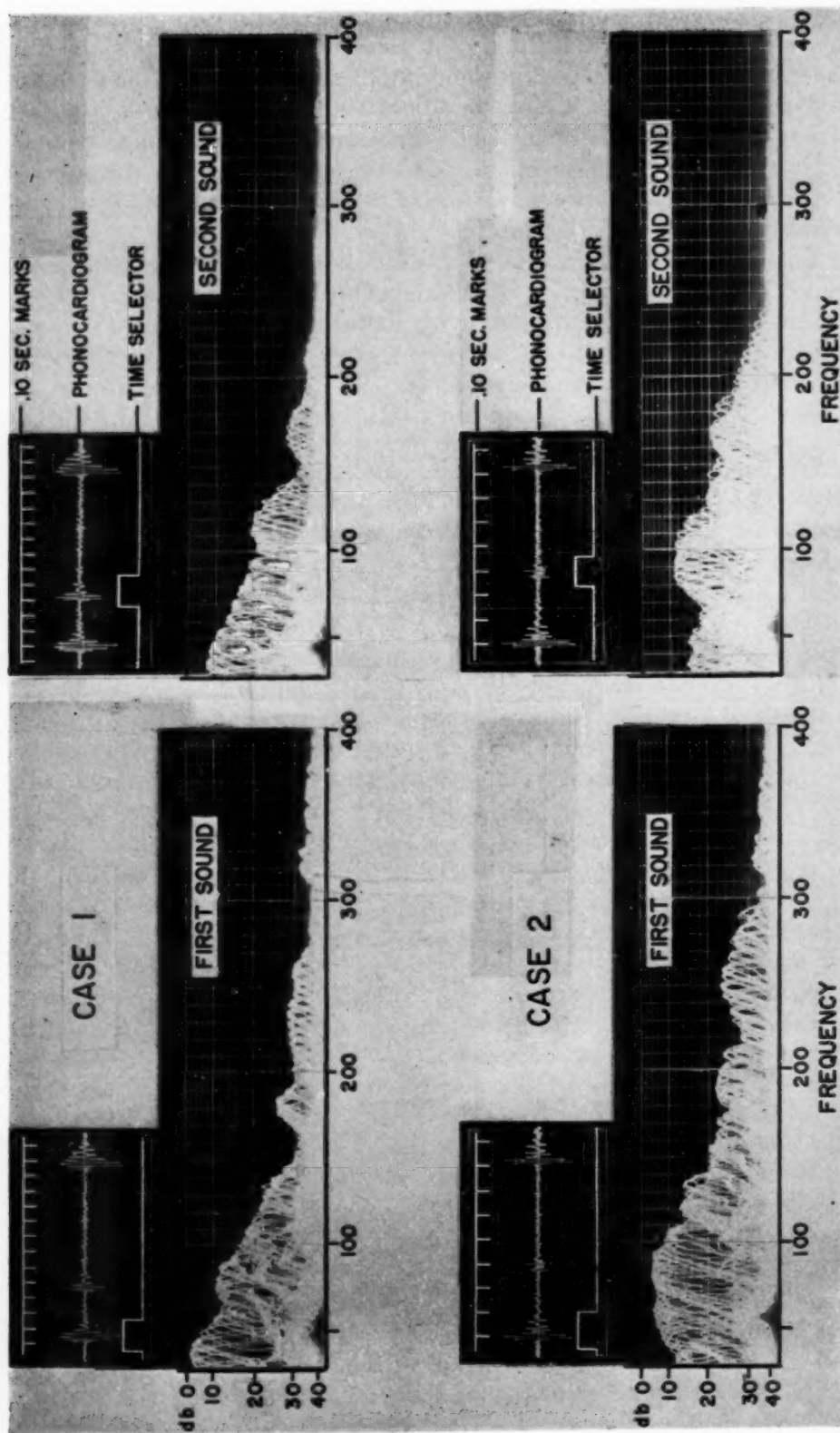


Fig. 2.—(Case 1.) Frequency spectra of heart sounds. Young medical student. Normal heart. Apex. (Case 2.) Sounds of another normal heart. P-R Interval 0.16 second. Apex.

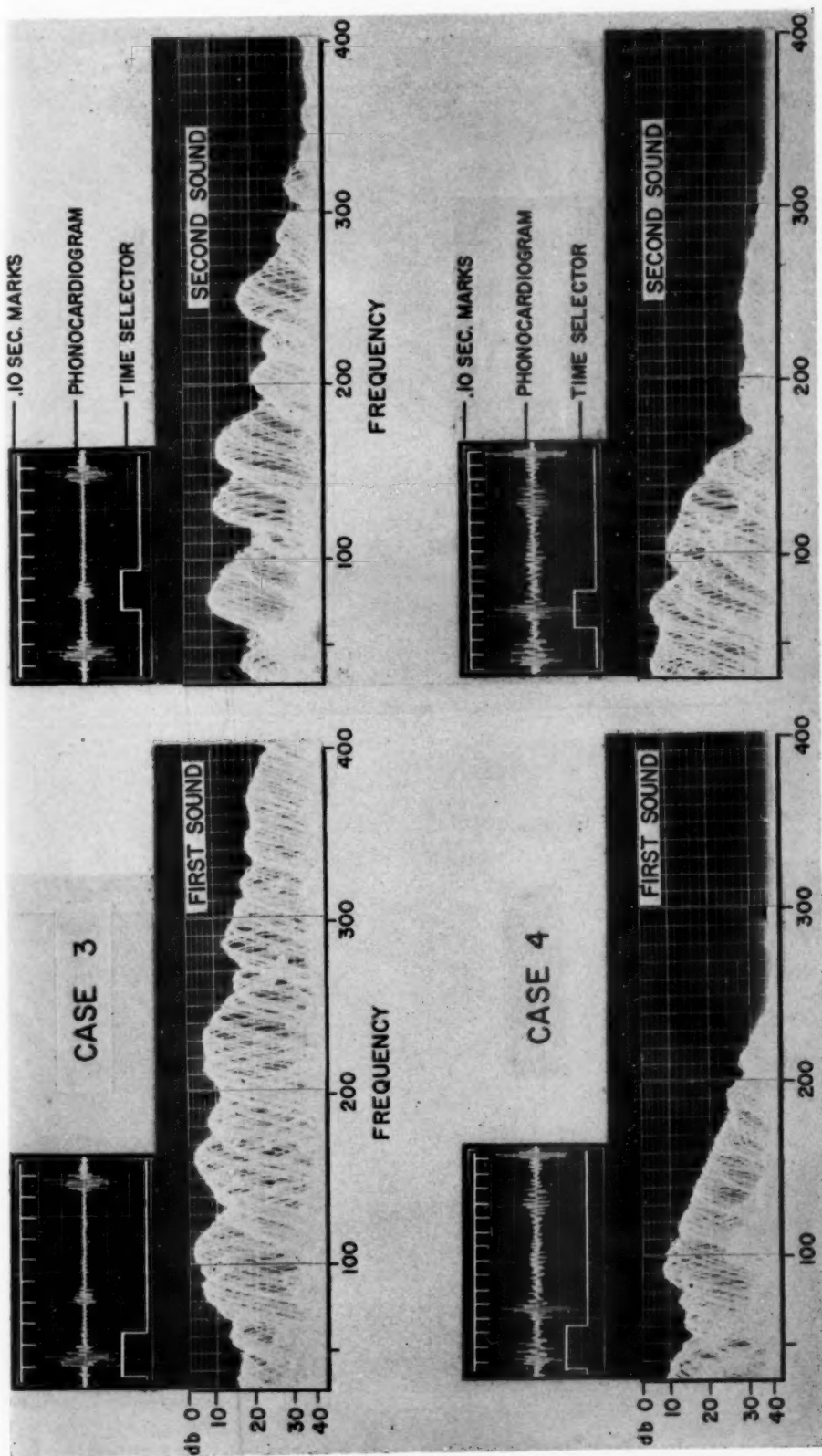


Fig. 3.—(Case 3.) Heart sounds of a normal 16-year-old boy. P-R interval 0.13 second. Apex. (Case 4.) Sounds of another normal heart. Relative lower intensity of first heart sound is related to the longer P-R interval (0.24 second). Apex.

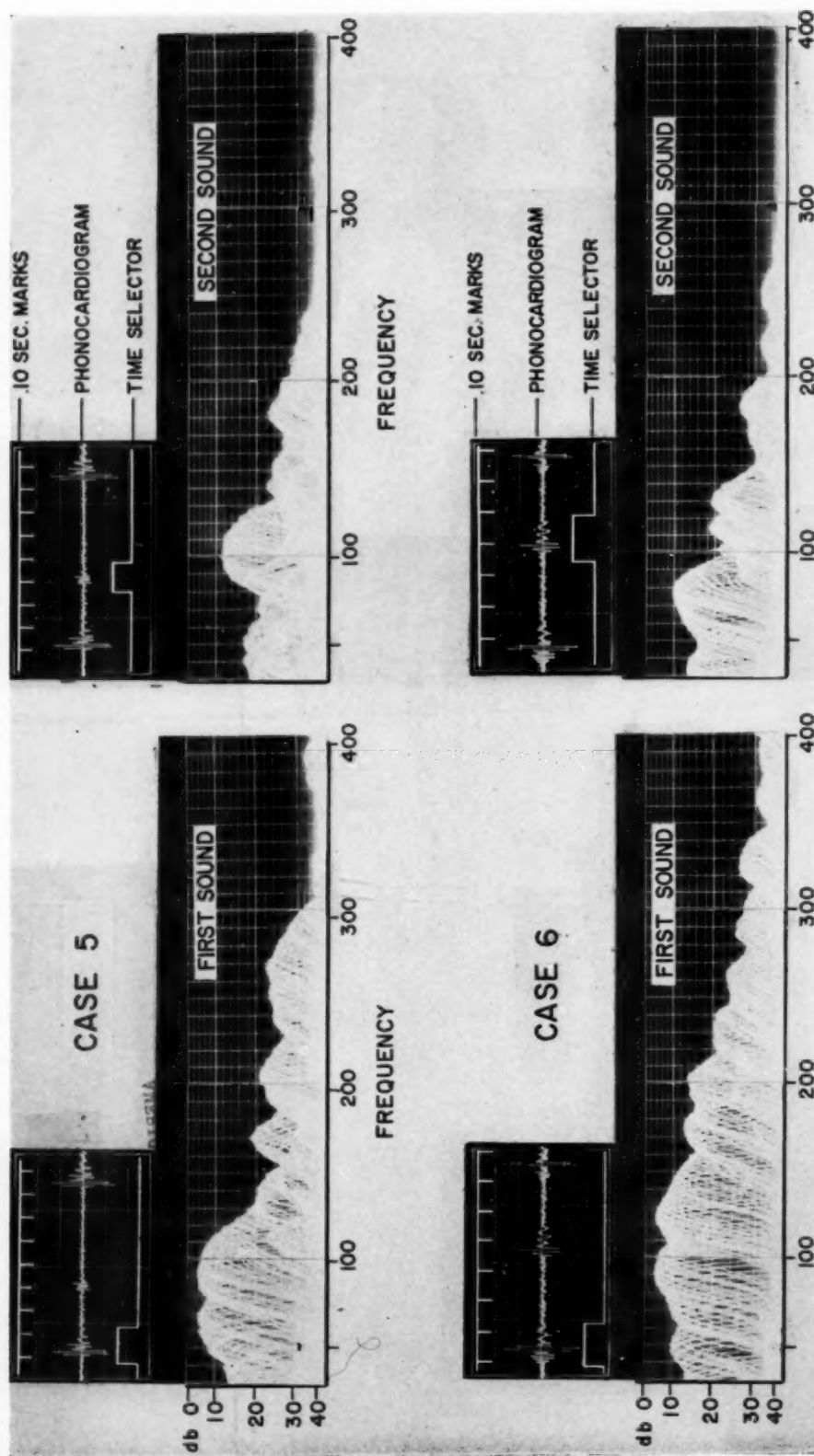


Fig. 4.—(Case 5.) Normal heart. Apex. (Case 6.) Heart sounds of 43-year-old man with fever and anemia. No heart disease. Apex.

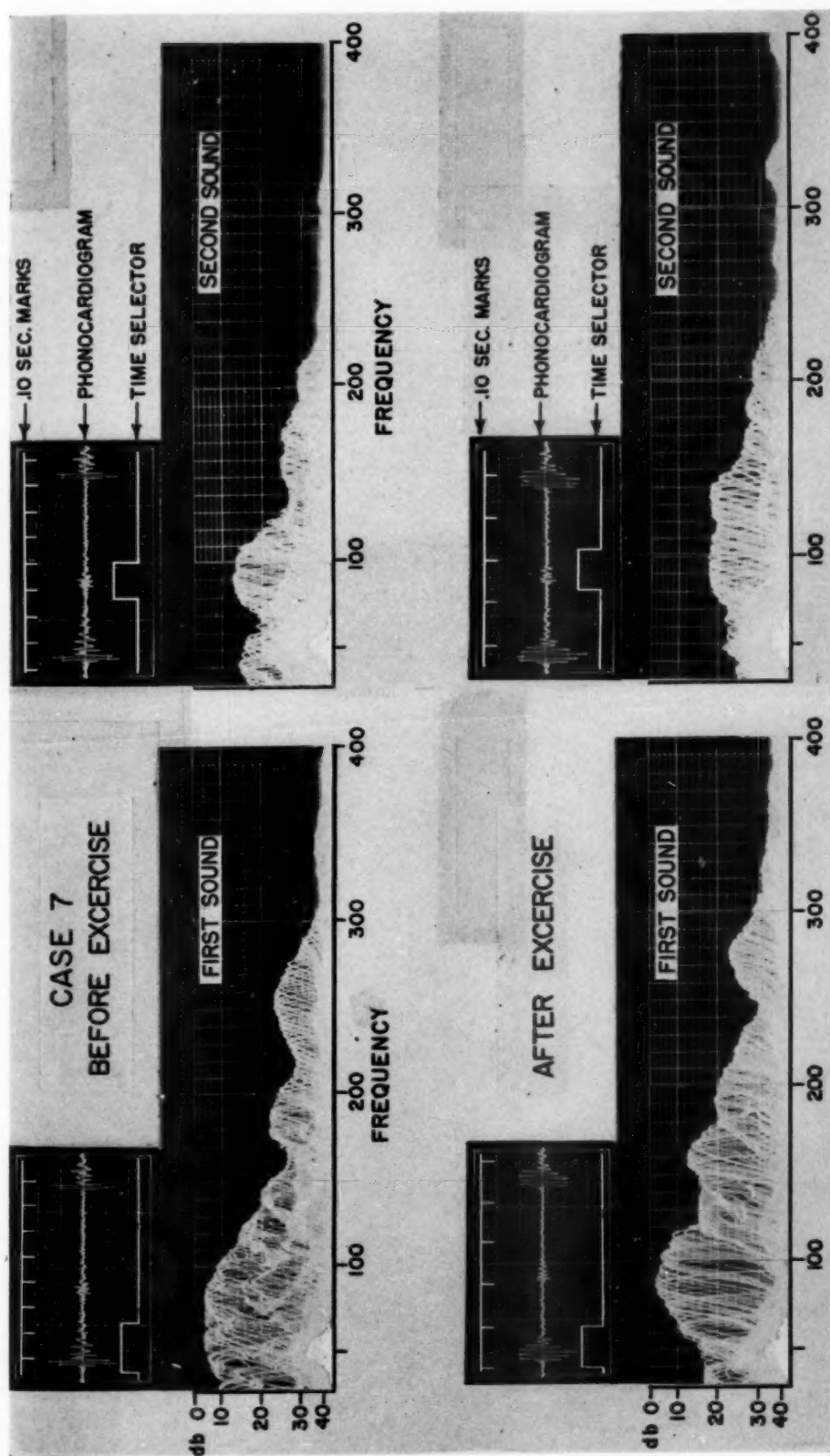


Fig. 5.—(Case 7.) Top, heart sounds of 35-year-old healthy man before exercise. Apex. Bottom, after exercise. Apex.

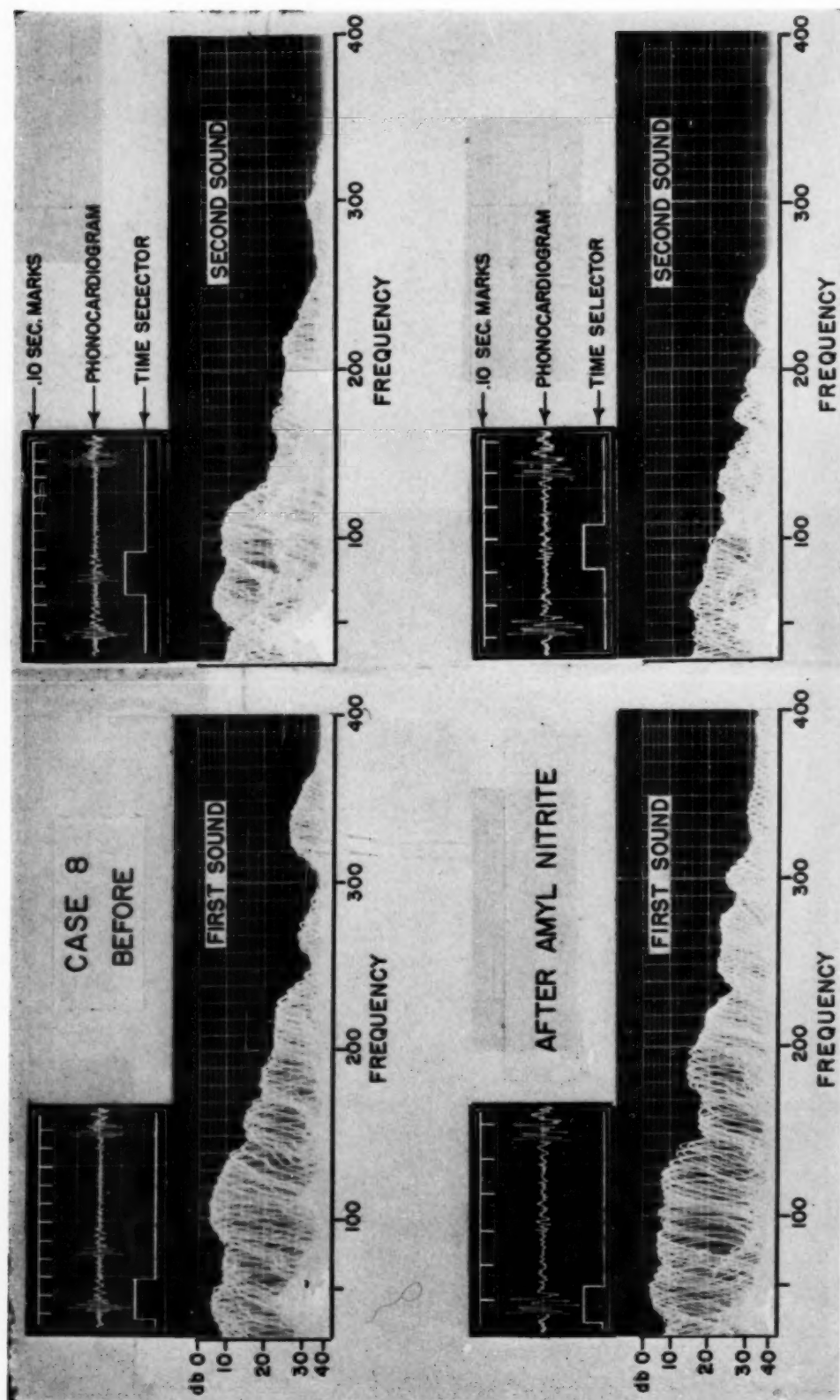


Fig. 6.—(Case 8.) Top, sounds of a normal heart. Apex. Bottom, same person after inhalation of amyl nitrite. Apex.

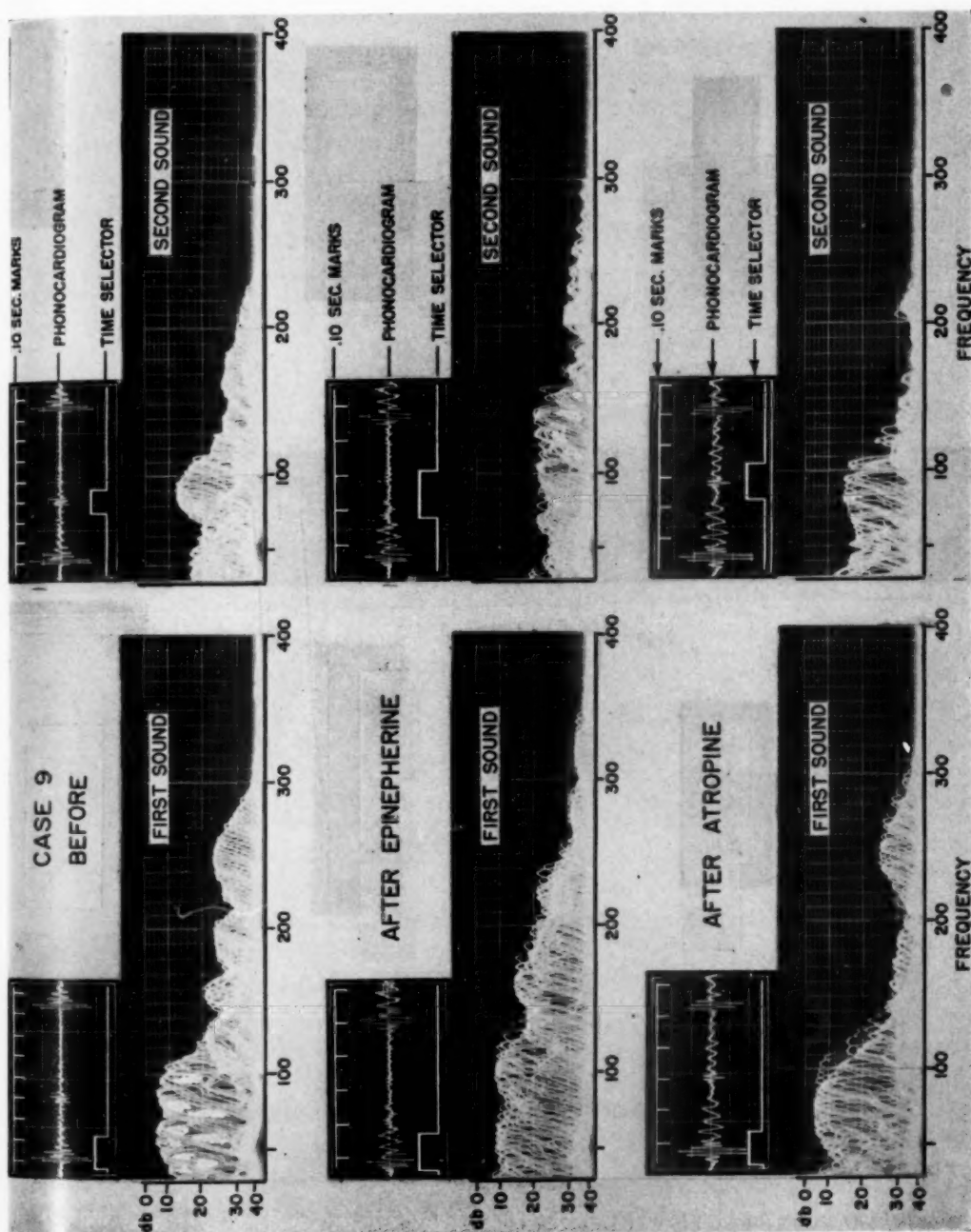


Fig. 7.—(Case 9.) Top, sounds of a normal heart. Apex. Middle, same person after injection of epinephrine. Apex. Bottom, same person after intravenous injection of atropine. Apex.

Figs. 4 to 7 show the frequency spectra of sounds produced by some other normal hearts under a variety of conditions.

Fig. 6 shows the frequency spectra of the first and second sounds of a normal heart before and after inhalation of amyl nitrite. Amyl nitrite produces dilation of the coronary vessels and other arteries followed by decreased work of the myocardium, and decreased blood pressure.

Fig. 7 shows the frequency spectrum of the first and second sounds of a normal heart before and after injections of epinephrine and atropine. Injections of epinephrine slow the flow of blood through the capillary vessels by producing a narrowing of arterioles and precapillaries. It also produces an elevation of blood pressure, ventricular tachycardia, and a slight shortening of relative and absolute refractory periods in atrial and ventricular musculature. Injections of atropine are followed by a fall in systolic pressure.

CONCLUSIONS

The over-all slope of the sound spectrum of a particular heart sound is dependent upon the abruptness of muscular contraction which in turn determines the rate of pressure change. Thus, the rate of rise of intraventricular pressure determines the over-all slope of the spectrum of the first heart sound. When peaks are observed in the sound spectrum they usually are harmonics of the fundamental vibrations of one or another of the primary valvular or muscular sound sources. Frequency peaks which are not part of such a harmonic series might possibly be produced by resonance effects in the arterial blood columns, resonant vibrations of tendinous structures, or by the presence of turbulence vortices (similar to edge tones) near the valves when the flow rate is sufficiently high. This might occur, for example, in the first sound, near the semilunar valves during the maximal ejection phase of systole. Such vortices could also conceivably occur near the auriculoventricular valves during the rapid filling phase in diastole.

SUMMARY

An experimental method has been described for obtaining the frequency spectra of heart sounds. Analyzed results are shown for some normal heart sounds. No attempt is made to correlate frequency peaks with specific sound sources since insufficient data is available and the mechanisms are imperfectly understood. A detailed frequency spectrum could conceivably be a valuable diagnostic tool if the various sound components could be related to specific cardiovascular mechanisms.

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SIMULTANEOUS LEFT VENTRICULAR AND AORTIC PRESSURE MEASUREMENTS IN THE EVALUATION OF AORTIC VALVE SURGERY

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STENOTIC lesions of the aortic valve are now amenable to surgical correction. The present report deals with a practical method for the determination of the hemodynamic effectiveness of corrective aortic dilatation in patients with aortic stenosis.

By comparing the pressures simultaneously obtained from within the left ventricle and the aorta at the operating table before and after surgery, two objectives may be achieved. It is possible (1) to appraise the physiologic significance of an aortic murmur, and (2) to assess the degree of relief afforded to the left ventricle by surgery.

PROCEDURE AND METHOD

All patients are intubated endotracheally and maintained under positive pressure respiration. They are anesthetized with intravenous pentothal and succinyl choline in conjunction with nitrous-oxygen supplement. The patients are placed in the left lateral position with the pericardium opened longitudinally. Pressures are now obtained with the left chest open, the atrial needle being inserted into either the auricular appendage or the atrial wall. The aortic needle is inserted into the arch of the aorta at approximately the origin of the left subclavian artery and is directed proximally. The ventricular needle is inserted into the left ventricle through its lateral wall.

The pressures are transmitted through the twenty-gauge, short-bevelled needles attached to specially-made, thick-walled saran tubing, approximately 24 inches long, with an outside diameter of $\frac{3}{16}$ inch, and an inside diameter of $\frac{1}{8}$ inch. They are connected to three Statham P23D pressure transducers, which are mounted in tandem at identical levels. The zero point is at approximately the mid-atrial level as determined by the operating surgeon. A five-channel single-beam cathode-ray photographic recording system is employed, embodying three pressure channels, one channel for the zero base line, and one for the electrocardiogram. The paper speed may be fixed at 25 or 75 mm. per second. The recording machine permits the direct superimposition of the three pressure tracings, simultaneously and synchronously, using a manometric system adjusted to equal sensitivity and identical base lines. The delay which is noted between the left ventricular and aortic pressure curves during ejection and

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protodiastole may be due to the presence of aortic stenosis. On the other hand, it may also be explained by the fact that the aortic needle is introduced at some distance from the aortic valve. Insertion of the needle into the wall of the left ventricle is routinely followed by several ventricular premature contractions which do not recur while the needle is in situ, and never necessitate the interruption of the procedure. There is no significant bleeding from the puncture sites at either the aorta, atrium, or ventricle. A minor jet of blood from the aortic puncture site is easily controlled by moderate pressure with a gauze sponge for a few minutes.

RESULTS

Simultaneous needle punctures of the aorta, left ventricle, and left atrium have been performed in twelve patients falling into three groups: (1) those with normal hearts, during surgical procedures within the left chest; (2) patients with mitral stenosis; and (3) in patients with combined mitral and aortic stenosis.

1. *Tracing of the Normal Cardiac Cycle.*—The normal cardiac cycle of the left side of the heart as described by Wiggers¹⁶ will be adhered to in these comments. Ventricular contraction begins with virtual simultaneous closure of the mitral valve, which marks the onset of isometric contraction. This consists of an initial slow phase followed by a rapid phase of pressure rise. In the normal heart, the rapidity of pressure rise increases progressively to the peak of ventricular systole (Fig. 4,A). The period of isometric contraction ends when the aortic valve opens. This is demonstrated graphically by the point at which the ventricular systolic pressure curve crosses that of the aorta. Aortic systole ends at the point of the incisura. There is no gradient between the ventricular and the aortic systolic pressures (Fig. 4,A and B) although there may be a slight lag between their peaks of systole. Isometric relaxation follows, and ventricular filling begins after the mitral valve reopens. This is indicated by the crossing of the ventricular and atrial pressure curves.

2. *Tracing of the Cardiac Cycle in Mitral Stenosis.*—In diastole, after the mitral valve opens, there is a pressure gradient between the left atrium and ventricle. This is somewhat higher during end diastole and is a measure of the physiologic significance of the stenotic mitral lesion. The period of left ventricular isometric contraction in mitral stenosis may, therefore, be subdivided into two phases, an initial one of left ventricular contraction with the mitral valve open, and a second of rapid increase in left ventricular pressure following closure of the mitral valve (Figs. 1,A and B and 4,A and B). Gordon and associates,¹ Moscovitz and associates,² and Braunwald and associates³ suggest the interesting paradox of filling of the left ventricle during its initial phase of contraction, because of the positive pressure gradient between the left atrium and ventricle (Fig. 1,B, point X).

Following mitral commissurotomy, the end-diastolic pressure gradient between the left atrium and ventricle is abolished (Figs. 2,A and B, and 5,A and B).

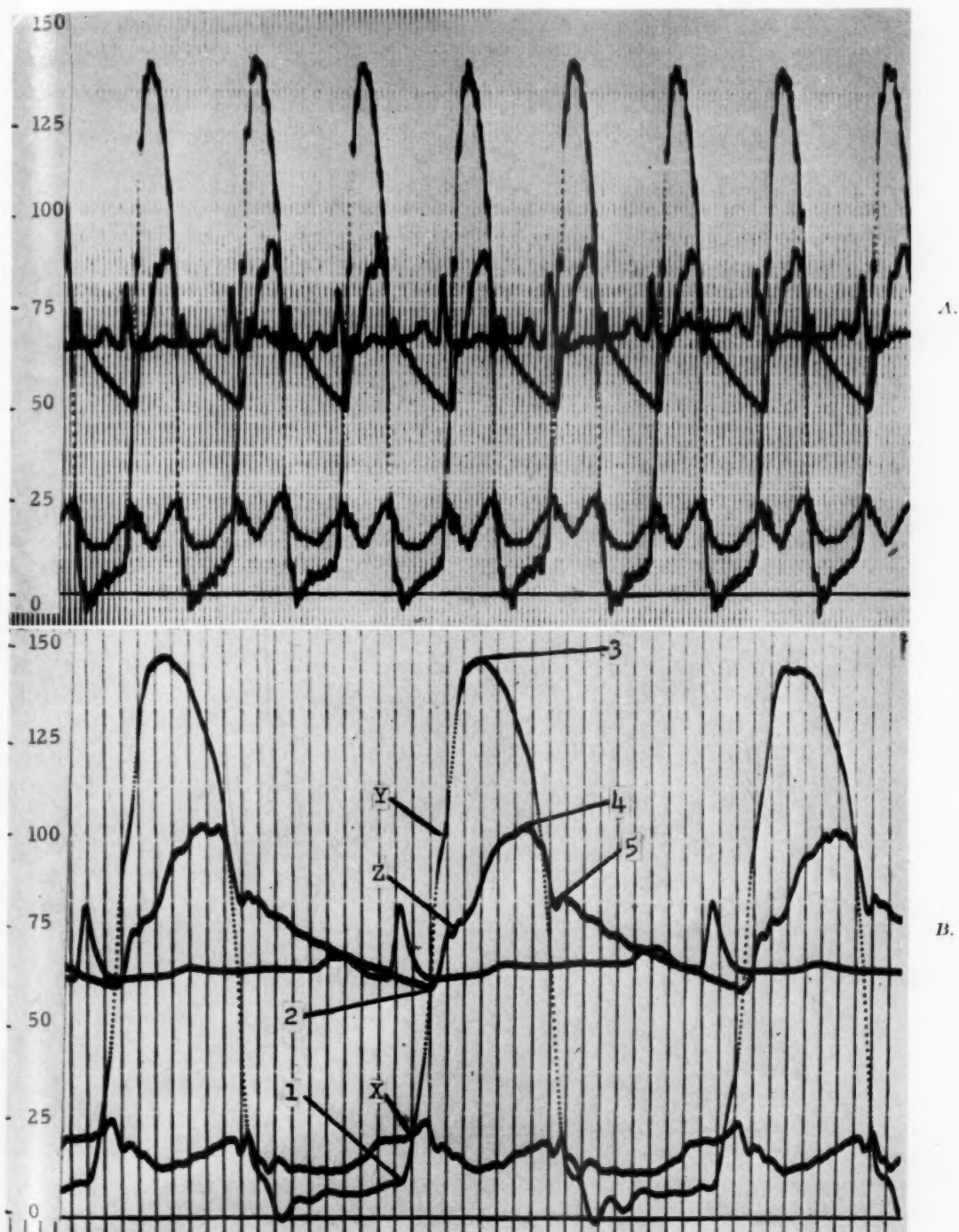


Fig. 1.—The cardiac cycle of the left side of the heart in a patient with combined mitral and aortic stenosis prior to surgery. A, Simultaneous pressure tracings with paper speed of 25 mm. per second. B, Same as above at paper speed of 75 mm. per second. Ventricular systole begins at 1 and mitral valve closure is represented at X. The auricular C wave begins at this time. Isometric contraction ends at 2, when the aortic valve opens. The period of maximum ejection lasts from 2 to 3, the peak of the ventricular pulse. This precedes 4, the peak of the aortic pressure pulse, which is delayed. Y represents the point of slowing of the rate of ventricular systole, and coincides with Z, the anacrotic notch on the ascending limb of the aortic pulse pressure tracing.

Note (1) The gradient between the end-diastolic left atrial and ventricular pressures, (2) the pressure differential between ventricular and aortic systolic pressure, and (3) the delay in their peaks of pressure.

3. *Tracings of the Cardiac Cycle in Combined Mitral and Aortic Stenosis.*—In the patients with combined mitral and aortic stenosis, the atrioventricular pressure gradient is similar to that described in pure mitral stenosis. The delay

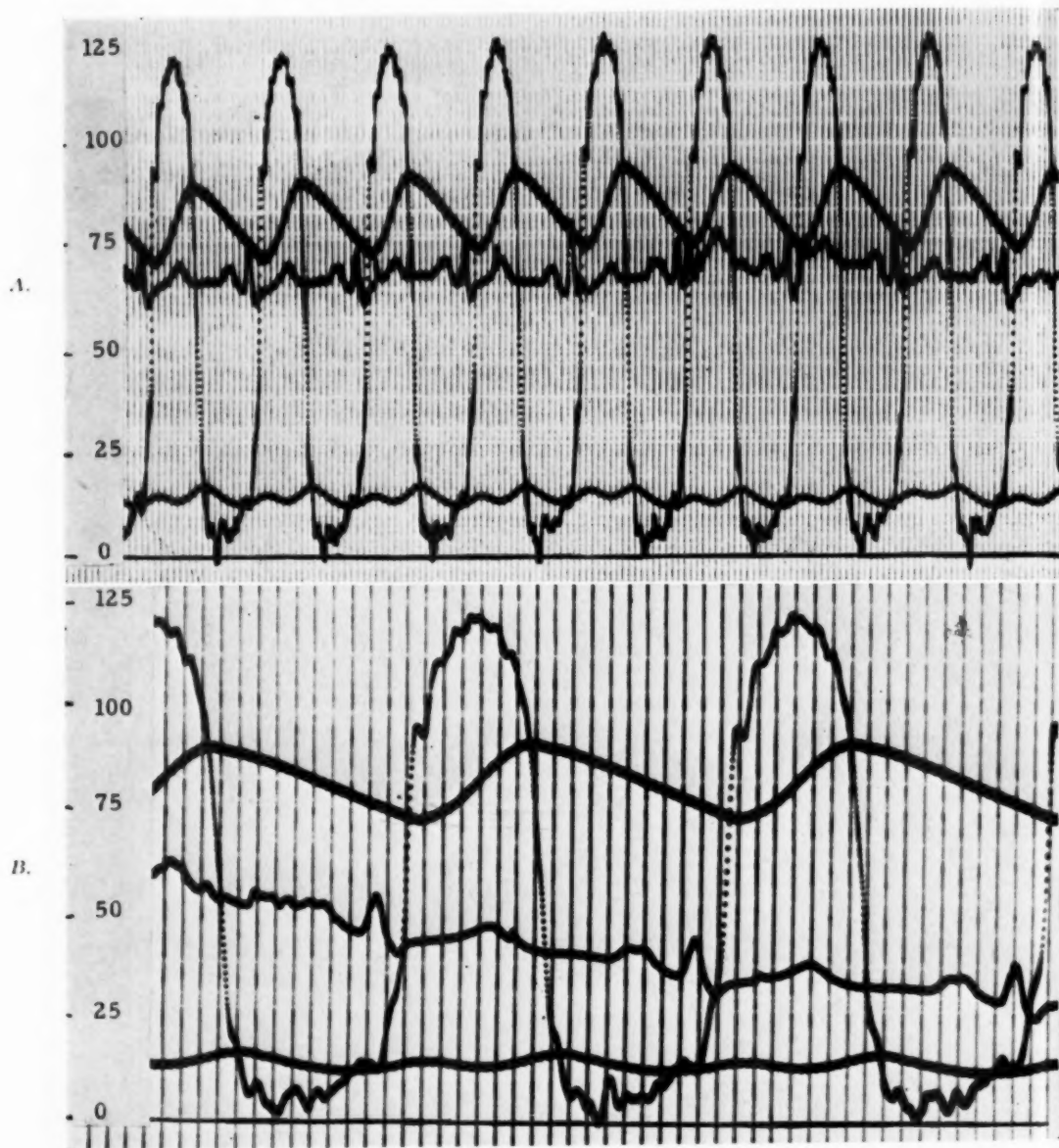


Fig. 2.—Cardiac cycle of patient (Fig. 1) after mitral commissurotomy and aortic dilatation. A, Paper speed at 25 mm. per second. B, Paper speed at 75 mm. per second.

The aortic and atrial pressures are somewhat damped. Note that (1) the gradient between the end-diastolic left atrial and ventricular pressures has been abolished, (2) the pressure differential between ventricular and aortic systolic pressure has been diminished, and (3) point Y of ventricular slowing is no longer manifest.

between the onset of ventricular systole and closure of the mitral valve measures 0.02 second (Fig. 1, A and B). The pressure curves obtained simultaneously from the left ventricle and aorta vary from the normal in two respects. First,

there is a significant gradient between their systolic pressures, and second, there is a delay between their peaks of systole (Table I). Of interest is the anacrotic notch in the aortic pulse pressure tracing, which has been described by Goldberg and associates.¹⁵ This notch on the ascending limb of the aortic pressure tracing coincides with a change on the ascending limb of the ventricular pressure tracing. Close inspection of the ascending limb of the ventricular pressure tracing (Fig. 1,B) reveals the following: Initially there is a slow phase of pressure rise, indicated by the line beginning at point 1 of ventricular contraction and ending where the tracing crosses that of the left atrium at point X. Here, the ascending limb of the ventricular pressure curve becomes a dotted line. Because of the characteristics of the recording machine, in which a single beam oscillates between all five channels, the rapidity of pressure change is indicated by the spacing of the dots. The dots become spaced farther and farther apart to the point of crossover of the ventricular pressure curve with that of the aorta. Approximately 0.02 second after the end of isometric contraction at point Y, these dots coalesce for 0.02 second, after which the tracing becomes dotted again. The coalescence of these dots is indicative of a 0.02 second period during which the rise in ventricular pressure becomes less rapid. It would appear almost as though the left ventricle paused to take a "second breath" immediately after the opening of the aortic valve. This period of "second breath" during ventricular systole probably produces the anacrotic notch (point Z) on the aortic pressure tracing. The period of ventricular slowing precedes the anacrotic notch on the aortic limb by approximately 0.02 second. This time lag may be due to the distance at which the needle is placed into the aorta from the level of the valve, and provides a base-line measurement for the lag between the pressure recordings of the ventricle and the aorta.

Next, there is a significant lag (measuring 0.1 second) between the peaks of systole of the ventricular and aortic curves. The peak of aortic systole coincides with the period of reduced ventricular ejection (Fig. 1,B). Normally, immediately after the aortic valve opens, there is a sharp rise in aortic pressure. In the patient with aortic stenosis, however, the rise in aortic pressure is gradual, and the aortic valve closes almost immediately after the peak of pressure is obtained (Fig. 1,A and B).

4. *Tracings of the Cardiac Cycle After Corrective Aortic Dilatation.*—After instrumental dilatation of the aortic valve, there is a marked decrease in the ventricular-aortic pressure gradient. In Case 1, before surgery, a ventricular systolic pressure of 148 mm. Hg produced an aortic systolic pressure of 94 mm. Hg. After opening the aortic valve, ventricular systolic pressure fell to 125 mm. Hg and was accompanied by a rise in concomitant aortic systolic pressure to 98 mm. Hg. (The aortic pressure tracing is damped and undoubtedly represents an even higher pressure.) In Case 2, prior to aortic dilatation, a left ventricular systolic pressure of 120 mm. Hg produced an aortic systolic pressure of 85 mm. Hg. After the aortic valve was opened, ventricular systolic pressure fell to 92 mm. Hg and was accompanied by an aortic systolic pressure of 82 mm. Hg. In both cases, there is a conspicuous fall in the ventricular-aortic gradient.

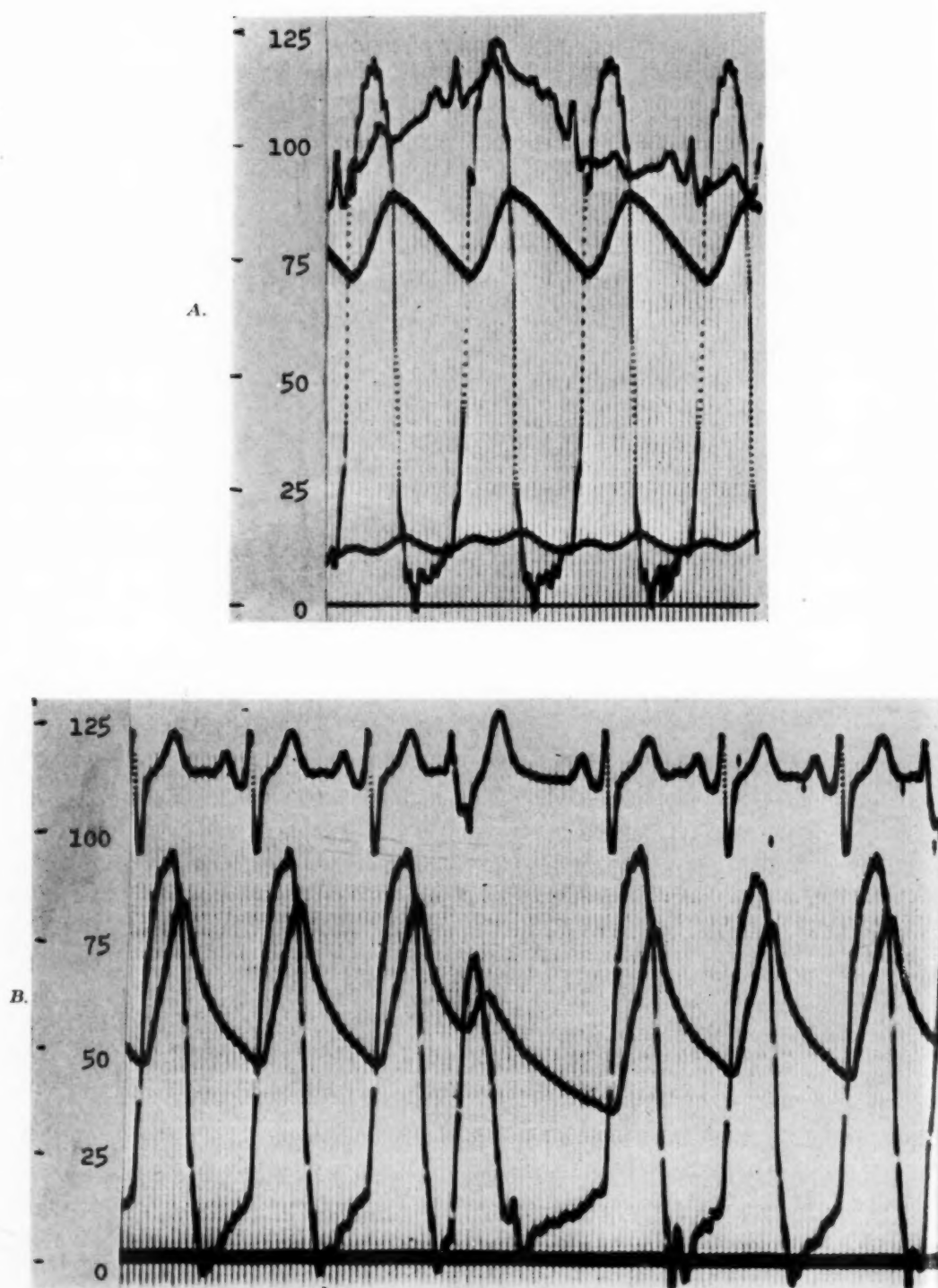


Fig. 3.—The cardiac cycle of the left side of the heart in a patient with combined mitral and aortic stenosis. *A*, Before surgery. *B*, After mitral commissurotomy and aortic dilatation. Note the marked diminution in the systolic pressure differential between the left ventricle and aorta after aortic dilatation.

TABLE I

PATIENT	LEFT ATRIAL PRESSURE	ATRIOVEN-TRICULAR FILLING GRADIENT	LEFT VENTRICULAR PRESSURE		AORTIC PRESSURE (SYST. — DIAST.)	LEFT VEN-TRICULAR AORTIC SYSTOLIC PRESSURE GRADIENT	DELAY IN LEFT VEN-TRICULAR AORTIC PEAK OF SYSTOLE (SEC.)	ISOMETRIC CONTRACTION		PERIOD OF MAXIMUM EJECTION	PERIOD OF REDUCED EJECTION	TOTAL TIME OF ISOMETRIC CONTRACTION	TOTAL TIME OF SYSTOLE
			SYST. — DIAST.	END-DIAST.				BEFORE M. V. CLOSURE	AFTER M. V. CLOSURE				
R. C. Preop. Postop.	25 13	17 0	148/2 125/2	8 13	94/54 98/78	54 27	.10 .12 (damped)	.02 .00	.04 .06	.12 .12	.14 .12	.06 .06	.32 .30
L. S. Preop. Postop.	14 0	(damped) (damped)	119/0 92/0	13 12	85/71 82/45	34 10	.12 .10		.08 .06	.16 .16	.12 .08	.08 .06	.36 .30

M. V. = Mitral valve.

Moreover, after aortic dilatation, there is a change in the timing of the systolic cardiac cycle. Prior to the correction of the mitral and aortic stenosis, isometric contraction lasted for 0.06 second and the time from the opening of the aortic valve to the peak of ventricular systole measured 0.12 second. Ven-

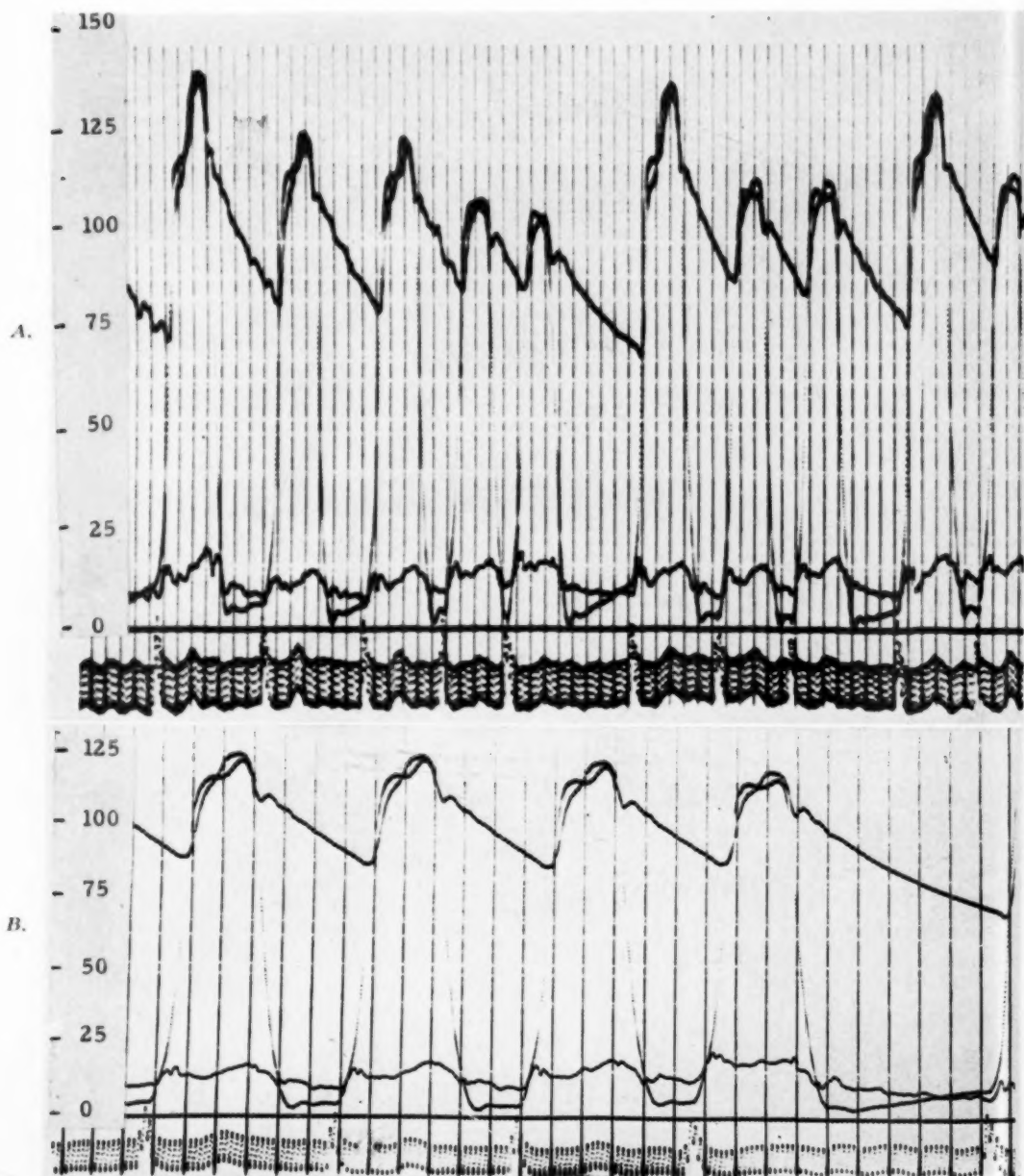


Fig. 4.—The cardiac cycle of the left side of the heart in a patient with mitral stenosis, and suspected, but nonexistent aortic stenosis, before surgery. A, Paper speed at 25 mm. per second. B, Paper speed at 75 mm. per second.

Note (1) The gradient between the end-diastolic pressures of the left atrium and the left ventricle, and (2) the absence of a pressure gradient between the left ventricle and aorta. This finding rules out the presence of a physiologically significant aortic stenosis.

tricular systole lasted for 0.32 second before, and 0.30 second after aortic dilatation. This difference is due solely to the shortened time between the peak of ventricular systole and the closure of the aortic valve.

5. *Tracings Indicating the Importance of the Ventricular-Aortic Pressure Gradient in the Diagnosis of Aortic Stenosis: Case History.*—M. W., a 32-year-old housewife, had a prolonged history of rheumatic polyarthritis in childhood. She was well until adult life, when she noted the onset of increasing and progressive

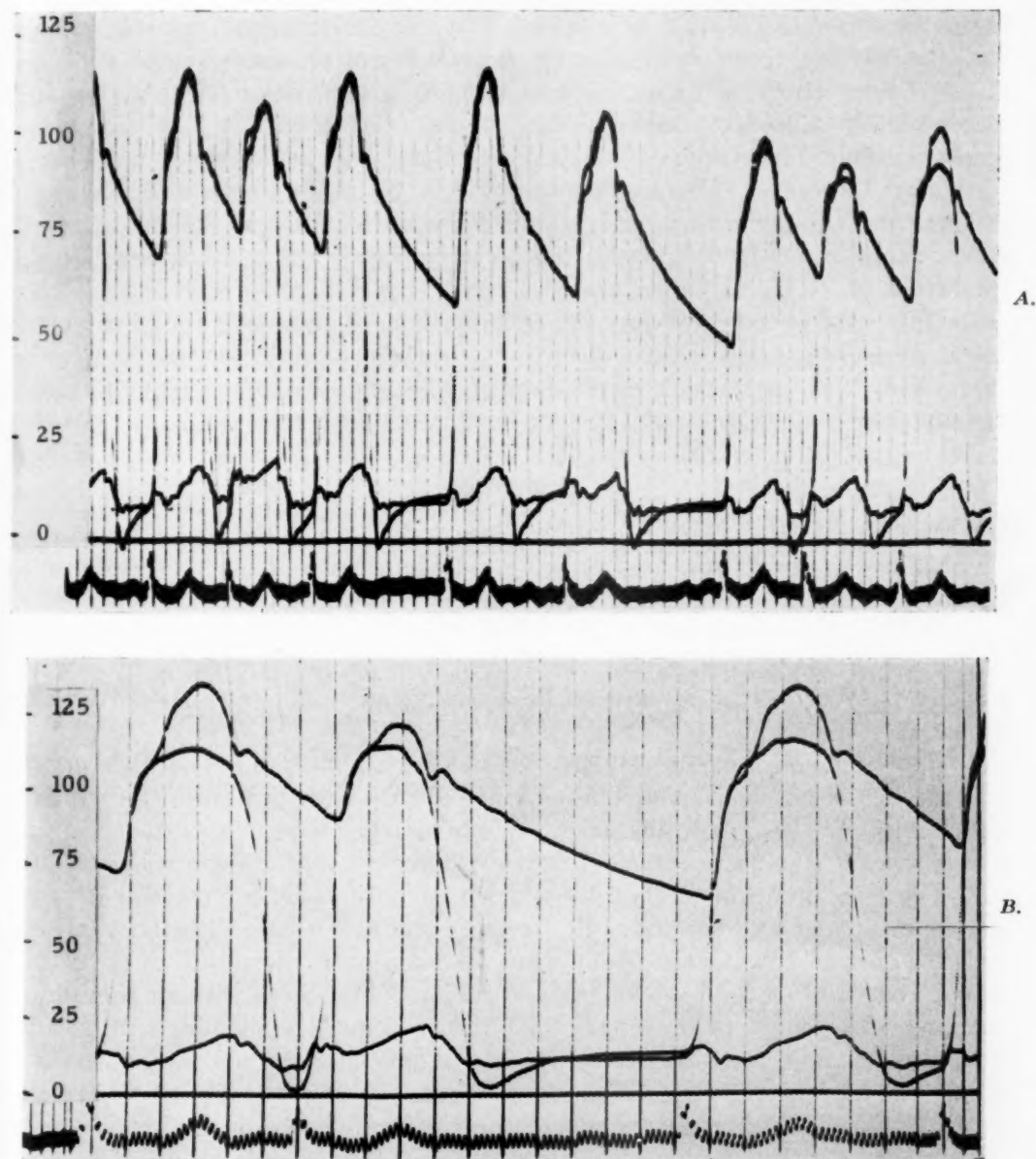


Fig. 5.—Same case as Fig. 4, after mitral commissurotomy. A, Paper speed at 25 mm. per second. B, Paper speed at 75 mm. per second. Note the abolition of the end-diastolic pressure gradient between the left atrium and ventricle.

exertional dyspnea. Except for the cardiac findings, physical examination was noncontributory. The mitral first sound was snapping. There was an apical mid-diastolic rumbling murmur. The pulmonic second sound was accentuated.

There was a rough systolic murmur in the second right intercostal space, not associated with a thrill. The aortic second sound was present but was diminished in intensity. On the operating table, a faint systolic thrill was palpated over the ascending aorta.

The pressure tracings (Fig. 4, *A* and *B*) taken at the time of surgery, revealed a significant pressure gradient between the left atrium and ventricle, which corroborated the diagnosis of mitral stenosis. However, there was no pressure gradient between the left ventricle and the aorta. The aortic systolic murmur was probably caused by eddies of flow across a pathologically involved aortic valve, without the presence of a hemodynamically significant stenosis. Therefore, after the mitral valve was opened (Fig. 5, *A* and *B*), aortic dilatation was not performed. This, of course, significantly reduced the operative risk and other complications which attend the performance of a transventricular aortic dilatation.

This case demonstrates the extreme importance of measuring the ventricular-aortic pressure gradient on the operating table before aortic valvular surgery is performed. It illustrates the error which may be made in attempting to diagnose the physiologic significance of a systolic murmur at the aortic area.

DISCUSSION

At the present time, the clinical response of the patient and the postoperative brachial arterial pulse pressure tracings constitute the two major means of evaluating the adequacy of aortic valvular surgery. Both methods are inadequate to scientifically evaluate the degree to which the mechanical obstruction to the aortic valve has been relieved. Moreover, the psychologic effect of cardiac surgery has been demonstrated to be a significant and frequently misleading factor.

Goldberg and associates¹⁵ have demonstrated that the anacrotic notch present in the brachial arterial tracing of patients with proved aortic stenosis may disappear after aortic dilatation. However, they were unable to quantitate the degree and significance of the stenosis. Moreover, the finding was inconstant.

The only practical method by which a stenotic lesion of the aortic valve can be evaluated is to determine the pressure gradient between the left ventricle and the aorta. Rheumatic cardiac patients may have deformities of the aortic valve, consisting of mild thickening and rolling of the cusps without significant stenosis. Deformity of the aortic valve per se is not synonymous with an obstructive lesion at that site, as it is possible to have an aortic murmur with little if any change in the ventricular-aortic gradient. Only in those patients demonstrating a significant gradient between the systolic pressure of the left ventricle and the aorta is there a physiologically significant aortic stenosis. Ideally, these results should be complemented by another variable, namely, determination of blood flow. This phase of the study was not projected for technical reasons, the objective being to establish a procedure which could be carried out readily and simply under operative conditions.

Left heart pressures have been measured sporadically. Wynn and co-workers,⁴ Connolly and his associates,⁵ and Bedell and co-workers⁶ have meas-

ured left atrial pressures at the operating table. Allison⁷ has measured pressures within the left atrium transbronchially, and Björk and Fisher⁸⁻¹¹ have measured pressures within this chamber by needling it through the right posterior thoracic wall. In a refinement of this technique, Fisher^{8,9} has utilized this needle for the insertion of fine polyethylene catheters into the left ventricle and aorta. Hansen and co-workers,¹² and Pederson and his associates¹³ have measured ventricular pressures at the operating table.

Gordon and associates¹ have devised an ingenious method by which left atrial, left ventricular, and aortic pressures are obtained by needle puncture in the open chest, and are inscribed simultaneously and synchronously using a manometric system adjusted to equal sensitivity, and with identical base lines. A record of the changes in pressure, as well as an accurate timing of the phases of the cardiac cycle may be obtained. In patients with mitral stenosis, a pressure gradient between the left atrium and ventricle is noted. It is highest at end diastole. This finding has been substantiated by the present investigation (Fig. 4, *A* and *B*). Moreover, the end-diastolic pressure gradient may be abolished by an adequate mitral commissurotomy (Fig. 5, *A* and *B*).

The method of simultaneously recording pressures from the cardiac chambers has been utilized in the current investigation of combined mitral and aortic stenosis.

A hemodynamically significant stenosis of the aortic valve must produce a systolic pressure gradient between the left ventricle and aorta. The measurement of this left ventricular-aortic pressure gradient at the operating table provides precise means of evaluating the severity of this lesion. Moreover, the effectiveness of the correction of the lesion can be evaluated by the abolition of the ventricular-aortic pressure gradient.

Conversely, in the absence of a significant left ventricular-aortic pressure gradient (Fig. 4, *A* and *B*), the diagnosis of a significant stenotic lesion of the aortic valve should be abandoned.

SUMMARY AND CONCLUSIONS

1. The urgent need for a practical method of evaluating the adequacy of corrective surgery for stenotic lesions of the aortic valve is emphasized.
2. The necessity for an accurate means of differentiating a physiologically significant from a physiologically insignificant aortic stenosis, on the operating table, is stressed.
3. A method for recording the pressure gradient between the left auricle, left ventricle, and the aorta by inscribing synchronous and simultaneous pressure pulses of the left heart is presented.
4. The presence of a left auricular-ventricular pressure gradient in patients with mitral stenosis is noted, and the abolition of this gradient by an adequate mitral commissurotomy is demonstrated.
5. The left ventricular-aortic pressure gradient present in patients with significant aortic stenosis is stressed, and its reduction by effective operative dilatation of the aortic valve is described.

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ARRIVAL TIME AND CALIBRATED CONTOUR OF THE PULSE WAVE, DETERMINED INDIRECTLY FROM RECORDINGS OF ARTERIAL COMPRESSION SOUNDS

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THE arterial sounds commonly utilized in the measurement of the blood pressure^{1,2} provide other valuable clinical information. For example, the intensities and durations of these sounds afford an appraisal of the volume of extremity blood flow.³ In atrial fibrillation, the sound varies with the duration of the previous filling period and therefore presumably with the stroke output.⁴

The present study shows that when the arterial sounds are recorded simultaneously with the electrocardiogram, the upstroke of a calibrated pulse wave can be constructed. Previously, intra-arterial puncture has been required to obtain similar data. The records also provide a measure of the time of arrival of the pulse wave at the artery and of the relative rates of transmission of the wave. These data have value in diagnosis and in the assay of procedures and drugs affecting hemodynamic states.

METHODS

A blood pressure cuff placed over the upper arm was inflated to a level higher than systolic. The arterial sounds produced as the cuff pressure was allowed to fall were picked up with a microphone and recorded on a phonocardiographic instrument (Fig. 1) (Sanborn or Cambridge). Lead II of the electrocardiogram was recorded simultaneously.

As the pressure in the cuff was allowed to fall continuously, its level was registered at intervals of 20 mm. Hg by introducing standardization impulses into the electrocardiographic tracings.

Records were obtained in the resting state, after tourniquet occlusion or exercise of the arm, after generalized exertion, and after the administration of vasoactive drugs.

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RESULTS

Control records were obtained on volunteers who had no history or evidence of cardiovascular disease. In twenty-four volunteers, the Q-K time (the interval from the onset of the QRS complex of the electrocardiogram until the onset of the sound at the brachial artery) averaged 0.21 second at diastolic pressure levels, and ranged from 0.16 to 0.25 second.

A plot of the Q-K time against the pressure in the cuff provided a trace similar in appearance to the upstroke of the arterial pressure pulse (Fig. 2).

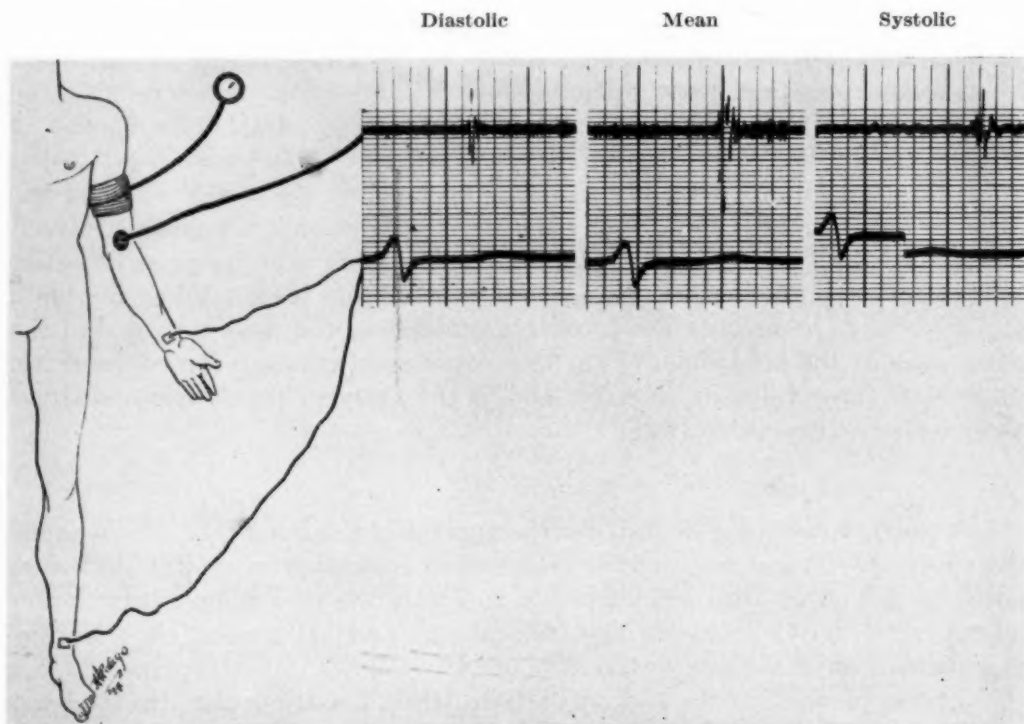


Fig. 1.—Schema showing the method of recording. The blood pressure cuff is placed in the usual position on the arm. A microphone transmits the arterial sounds to a phonocardiographic machine which records the acoustic tracing and the electrocardiogram simultaneously. Three cuttings from a representative tracing are given. The strip at the right shows the time required for arrival of the sound at systolic pressures, in this case being 0.36 second from the onset of the electrocardiographic QRS (Q-K time). The middle strip taken at mean pressure shows a Q-K of 0.25 second. The strip to the left, taken at diastolic pressures, shows a Q-K of 0.21 second.

Popliteal Artery.—In five subjects the Q-K time at the popliteal artery was determined. The popliteal Q-K interval at diastolic pressure levels was considerably longer than that obtained for the same level at the brachial artery, averaging 0.32 second. The derived slope of the upstroke at the popliteal artery was somewhat steeper than tracings obtained at the brachial artery of the same patient.

Validation Experiments.—In six subjects the direct pressure pulse was recorded on a Sanborn Poly-Viso with a needle in the brachial artery immediately distal to the pressure cuff; the Korotkoff sounds and an electrocardiogram were inscribed simultaneously (Fig. 3).

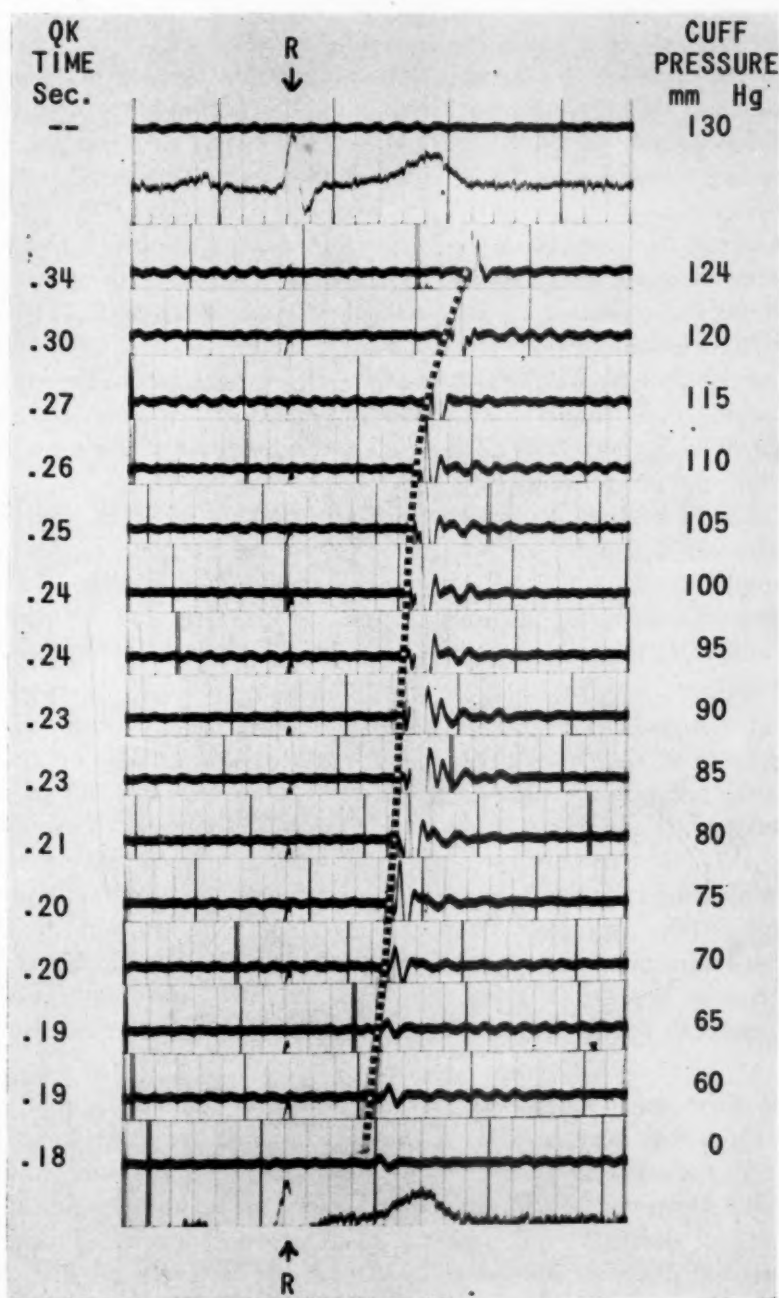


Fig. 2.—Progressive prolongation of the lag from the electrocardiographic QRS until the time of onset of sound in a normal subject. Each heavy horizontal line represents a cardiac cycle. The successive horizontal lines shown were recorded as the cuff pressure was lowered by increments of 5 mm. Hg. The peak of the R wave indicated by the arrows has been used to line up each of the successive strips. The vertical dotted line joins the onset of each of the sounds, providing an indirect representation of the upstroke of the pulse wave. The Q-K for each cuff pressure level is given in the column at the left; the cuff pressure for each strip is given in the column at the right.

When the cuff pressure was set higher than the systolic pressure, neither a pressure pulse nor a sound was registered, as expected. When the cuff pressure was permitted to fall to systolic levels, a slight rise at the peak of systole was inscribed on the pressure tracing obtained directly from the artery distal to the cuff. The onset of this pressure rise began almost synchronously with the beginning of the inscription of the sound*; this relationship between the onsets of pressure rise and arterial sound was constant for all cuff pressure levels between systole and diastole.

It was noted that as the cuff pressure fell, both the onset of the pressure rise and the onset of the sound occurred earlier and earlier with reference to the QRS of the electrocardiogram. This relationship has been recorded by others, but its significance has not been commented upon.^{5,6}

A plot of the time from the onset of each QRS to the onset of the immediately following sound (Q-K time) against the cuff pressure for each recorded beat yielded a curve with the proper time relation and contour of the ascending limb of the arterial pressure pulse at that site.

Effect of a Tourniquet on the Extremity.—In eight subjects, tourniquet occlusion of the blood supply to the arm distal to the microphone had no effect on the timing of the sound. The sounds were markedly diminished in intensity, in consonance with our previous findings that the intensity and duration of these sounds are related to the volume of blood flowing through the compressed arteries under the cuff.³

Effect of Exercise of the Extremity.—After inflation of the cuff to a pressure higher than systolic, the fist of the same arm was opened and closed thirty times in about thirty seconds to induce a reactive hyperemia. The cuff pressure was then allowed to fall and the sounds were recorded as above. Under these circumstances the intensity and the duration of the sounds were considerably increased in all subjects tested, in accordance with the expected enhanced blood flow induced by the exercise. However, the Q-K time and the derived pulse wave contours were unaffected by the presumed local increase in blood flow.

These results suggest that the Q-K time and the pulse wave contours are probably unrelated to the volume of blood flow through the extremity being studied.

General Exercise.—Generalized exertion such as vigorous hopping in place for two minutes was performed in eighteen experiments. The heart rate was usually but not always increased. The diastolic blood pressure was changed little, if at all. However, in all tests, there was a consistent reduction in the Q-K time not only at diastolic, but at all arterial pressure levels. The mean Q-K time at diastolic pressure immediately after exercise averaged 0.18 second, a reduction of 0.03 second from that obtained in the resting state.

At cuff pressures greater than diastolic the Q-K times were shortened even more. As a result, the slope of the upstroke of the pulse wave was considerably steepened in the immediate postexercise period. As the subject recovered from

*In most of the records the onset of the sound preceded the pressure rise by approximately 0.01 to 0.02 second. This is due in part to the lower position of the intra-arterial needle in our experiments and to the intrinsic time lag of the manometer system.

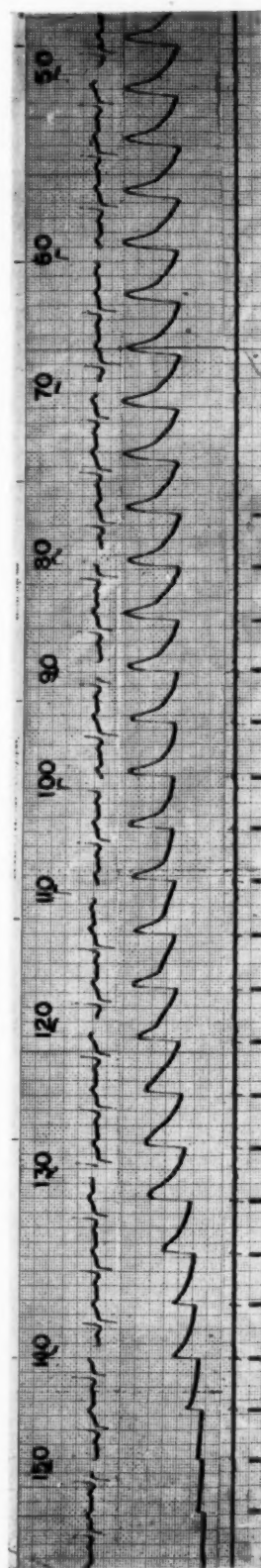


Fig. 3.—A continuous trace showing simultaneous recordings of the electrocardiogram, the intra-arterial blood pressure immediately distal to the cuff, and the sounds at the brachial artery. The short vertical lines at the bottom of the record point to the bursts of sound which are poorly demarcated. As the cuff pressure is permitted to fall continuously, the electrocardiographic tracing is interrupted by standardization impulses, the cuff pressure at each being noted in the numbers given. It can be seen that the sound appears almost immediately in advance of the rise in pressure in the needle in the adjacent artery.

the exercise, the time of onset and the slope gradually became prolonged, and after a few minutes returned to the resting values.

Epinephrine.—Commercial epinephrine (Parke, Davis) (0.03 mg.) administered intravenously or intramuscularly, reduced the Q-K time and steepened the pulse wave contour (Fig. 4). With the onset of the pressor response, the average Q-K time at diastolic pressure levels was reduced by an average of 0.04 second, and by as much as 0.07 second. The slope of the upstroke was increased similar to that observed after generalized exercise. This indicated that at systolic levels a still greater reduction was produced in the Q-K time than that which

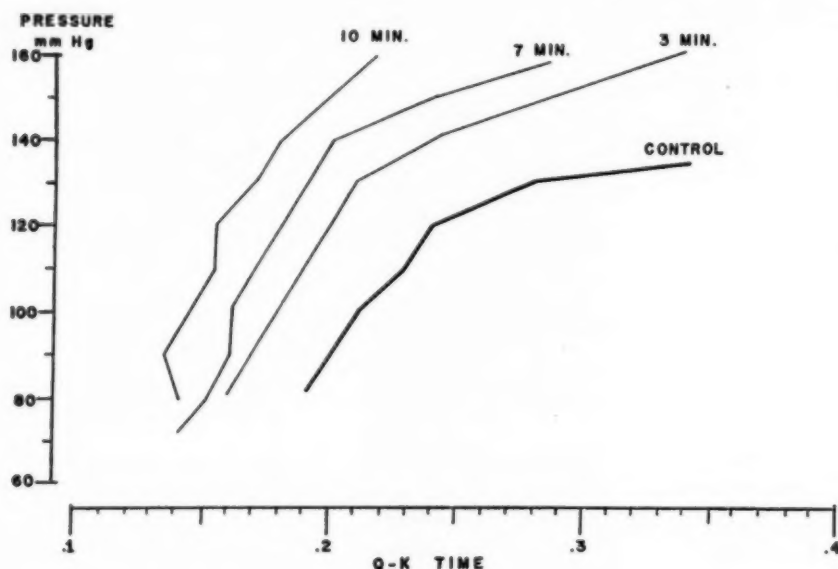


Fig. 4.—The effect of intramuscular epinephrine on pulse wave contour and arrival times obtained by the method described. The heavy line represents data obtained in three successive runs on an individual at rest. The three lighter lines represent the tracings obtained at three, seven, and ten minutes, respectively, following injection. The Q-K time is significantly shortened, the systolic pressure raised, and the steepness of the curve increased. Discussed in text.

occurred at diastolic pressure levels. As the effects of the drug wore off, the Q-K time at all pressure levels was progressively prolonged, returning to normal in approximately four minutes in those experiments in which the drug was given intravenously. A more prolonged course was seen after intramuscular injection (Fig. 4).

Norepinephrine.—Intravenous injection of norepinephrine (0.03 mg.) raised both the diastolic and systolic pressures and decreased the Q-K time, but to a lesser degree than did the intravenous epinephrine. As with epinephrine and exercise, an enhanced slope of the upstroke was also observed.

Amyl Nitrite.—Inhalation of a pearl of amyl nitrite in eight subjects was followed by a brief tachycardia and hypotension, and the diastolic Q-K time was usually but not consistently shortened.

DISCUSSION

The foregoing results demonstrate that a calibrated contour of the ascending limb of the pulse wave, as well as timing of the arrival of the pulse wave during the cardiac cycle, may be obtained by indirect means. Such data may have value for clinical, diagnostic, and experimental studies on the effect of various procedures affecting these measures of the cardiovascular system.

Methods for obtaining pulse wave contours by application of a pelote over a vessel have long been available, but the tracings so obtained cannot be calibrated in terms of millimeters of mercury. Instead, they represent movement of the arterial wall under force of the pressure, but no satisfactory method is available for conversion of these movements into pressure readings. A calibrated contour is obtainable by intra-arterial puncture or cannulation, but the difficulties and hazards of these procedures necessarily limit their use.

Our experiments in which the intra-arterial blood pressure was recorded simultaneously with the arterial sounds demonstrated that the occurrence of the sound is related to the flow of blood through the arteries compressed by the cuff. This is indicated by the fact that the sound is associated with an almost simultaneous pressure rise in the needle beyond the cuff.

The results obtained in the experiments utilizing a tourniquet, or after reactive hyperemia, show that the volume of blood flow through the extremity has no significant effect on the time of arrival of the pressure pulse or its contour. This must mean that changes in the arrival time or the contour must depend on factors operating in the heart or in the aorta and its branches.

In each cardiac cycle, the Q-K time between the Q wave of the electrocardiogram and the arrival of the pressure pulse or sound production (K) at a distal artery may be divided into two intervals: (1) the Q-E time: from the onset of the electrocardiographic Q wave until the onset of ejection (E) at the aortic valve, and (2) the E-K time, required for transmission of the pulse wave from the aortic valve to the point of sound production under the cuff.

The Q-E time is approximately 0.08 second⁷⁻⁹ in most published records, and in the experience at the Michael Reese Hospital Heart Station.

If this value (0.08 second) is subtracted from the Q-K time, a time period probably representing the transmission time (E-K) of the pulse wave is obtained. On the basis of data at present under analysis, an average E-K time of 0.13 second may be calculated for normal adults at rest. For a distance of 40 cm. from aortic root to brachial artery above the elbow, this average time would give a pulse wave velocity of approximately 3 meters per second, a value consistent with estimates based on other techniques.

Shortening of the Q-K interval suggests an increased celerity of pulse wave transmission. An exact measure of this acceleration is not certain since the Q-E time may also change, but other data suggest that the Q-E time cannot be shortened significantly. It would appear, therefore, that a diminution of the Q-K time probably represents an enhanced pulse wave velocity.

In our experiments, generalized exertion or the administration of nor-epinephrine or epinephrine all consistently shortened the time of arrival of the

pulse wave at the brachial artery and at the popliteal artery. These procedures also increased the slope of the ascending curve, indicating a more rapid wave transmission rate at the higher pressures. Since the cardiac output is increased in all three of these conditions, it may be suggested that an increase in stroke output increases the rate of transmission of the pulse wave. Other studies have provided further evidence for this concept.⁴

The present technique provides a safe, simple, indirect method for obtaining cardiovascular data of considerable experimental and clinical value. Its further study in various physiologic and pharmacologic conditions and in diseased states is indicated.

SUMMARY

A new, safe, indirect method for obtaining a calibrated ascending limb of the arterial pulse wave and its arrival time at the site of measurement is described.

The time from onset of the Q wave of the electrocardiogram until the registration of the arterial compression sound of Korotkoff (Q-K time) is shown to be related to the arrival time of the pulse wave at the artery under the cuff. A plot of the Q-K time against the pressure in the sphygmomanometer cuff permits the construction of a calibrated contour of the pulse wave. This relationship was confirmed by intra-arterial puncture techniques.

The Q-K time is unaffected by changes in the blood flow through the extremity compressed by the cuff.

The Q-K time is shortened and the slope of the upstroke is made more steep by generalized exertion, epinephrine, and norepinephrine. Analysis suggests that the shortening and the change in slope may be manifestations of an increase in pulse-wave velocity.

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PULMONARY STENOSIS WITH CLOSED VENTRICULAR SEPTUM

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AMONG the pulmonary stenoses with closed ventricular septum, we can distinguish two types, in accordance with the existence of a patent foramen ovale or a true interauricular defect (Fallot's trilogy of the French authors) or the interauricular septum being entirely closed (pure pulmonary stenosis). The fact that both types are amenable to the same intervention (direct valvulotomy), in contradistinction to the cases of pulmonary stenosis with overriding aorta (tetralogy of Fallot), in which is also the possibility of applying another type of intervention (systemic-pulmonary shunt), which is a contraindicated intervention if the ventricular septum remains intact, gives the reason for the grouping, for this study, of all the pulmonary stenoses with a closed ventricular septum.

This type of pulmonary stenosis has been seen to appear lately with relative frequency (Campbell,¹ Sobin,² and others³⁻⁶). In almost all the cases, the stenosis is of the valvular type, dome shaped,^{1,3,7,8} but it may be also of the infundibular or the double type.⁹⁻¹¹ This last fact is an argument against the general belief that the pulmonary stenosis that is of our concern is the consequence of a fetal endocarditis. Besides, the fact that the pulmonary stenosis may be associated with other congenital anomalies establishes another argument. As Allanby and Campbell¹¹ already pointed out, in 1949, likewise Whillis, that the pulmonary stenosis is, different from many congenital cardiopathies, a disturbance caused by embryonic overdevelopment, rather than a failure of development.

MATERIAL AND METHODS

A selection has been made of fifteen cases of pulmonary stenosis with closed ventricular septum. In seven of these, it was not possible to expose any anomaly other than the pulmonary stenosis. In six cases there was a patent foramen ovale or an atrial septal defect. In another case, a double superior vena cava was demonstrated, the left one draining into the left auricle, causing an arteriovenous shunt. Finally, in another case, there was a partial drainage of the pulmonary veins into the right auricle, this constituting the only case in our series of pulmonary stenosis with arteriovenous shunt.

In all of them, a careful clinical, radiologic, and electrocardiographic study has been carried out, obtaining, besides the usual leads, two or three extreme right precordial leads. In seven of the cases, there was performed a ballistocardi-

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ographic tracing, and in six, a phonocardiographic recording was obtained. In thirteen cases, cardiac catheterization was carried out by the usual method, the pressure tracings being recorded with the Sanborn electromanometer connected to a Cambridge string electrocardiograph. The analysis of the oxygen content of the blood samples was done with the apparatus of Van Slyke, modified by Monche, and the oxygen consumption with a regular metabolimeter. In seven cases an angiocardigraphic study, in an anteroposterior position, could also be done, obtaining six exposures within eight seconds. The injection of the 70 per cent iodine contrast was performed with a pressure injector by means of a canula introduced into a forearm vein. The quantity to be injected was proportional to the weight of the patient.

Six patients were submitted to a transventricular pulmonary direct valvulotomy of the Brock type. One of the patients died as a consequence of the intervention. In this case, and in another patient who died from cardiac failure, necropsies were performed.

RESULTS

Clinical.—Table I.

Age and sex: The age ranged between 2 and 44 years, with an average of 16. No predominance was observed with regard to sex; seven were males and eight females.

Development: In two-thirds of the cases, the development was normal. Of the five cases with stunted growth, in four there existed a venous-arterial shunt with cyanosis; in three of them it was through the patent foramen ovale, and in the other, by means of a left vena cava draining into the left auricle. The remaining case was the most severe pulmonary stenosis of our series, the anatomic integrity of both septa being proved by autopsy. The degree of pulmonary stenosis was so severe that it allowed merely the passing of a thin probe through the valvular orifice.

Cyanosis: Cyanosis appeared in eight cases; in four, owing to the patency of the foramen ovale; in another, due to the draining of a left vena cava into the left auricle. In two cases, the cyanosis was of the peripheral type and coexisted with cardiac failure, and in the last, notwithstanding the fact that neither by cardiac catheterization nor by angiocardigraphy could be ascertained the existence of communication between the atria, the absence of cardiac failure suggested a right-to-left shunt as the origin of the cyanosis.

The apparent age of the cyanosis when it was due to a shunt oscillated between one and four years of age. In some cases the cyanosis was observed only while crying.

In two cases, where the existence of an atrial septal defect could be verified, the cyanosis had not appeared at 2 and 10 years of age.

In the two cases of cyanosis of the peripheral type, this appeared at 3 years of age in Case 6, and at 38 years of age in Case 14. Only two of the cyanotic patients of the central type presented squatting.

Syncope: Four of our cases presented syncope: three of them while on occasional exertion. In another case, it has shown up on various occasions. In these cases there existed in one of them a cyanosis of the central type, and in the other, a cyanosis from cardiac failure. The other two cases showed pure pulmonary stenosis. Only in the case with arteriovenous shunt, the syncope was accompanied with paroxysmal cyanosis.

Pulmonic infections: The rarity of repeated respiratory infections among the patients of our series has to be pointed out. The appearance of these infections could be verified only in three cases. In one of the patients there existed an anomalous draining of the pulmonary veins into the right auricle, giving place to the consequent arteriovenous shunt. In the other two patients there existed a right-to-left shunt. In one case it was produced through a patent foramen ovale, and in the other, owing to a persistent left superior vena cava draining into the left auricle.

TABLE I. CLINICAL DATA

	AGE	SEX	DE- VELOP- MENT	CYANOSIS (AGE OF APPEARANCE)	SQUAT- TING	SYN- COPES	RESPIRA- TORY INFEC- TIONS	F.C.	ARTE- RIAL PRES- SURE	CARDIAC EXAMINATION				DIAGNOSIS	VERI- FICA- TION
										H.F.	THRILL	S.M.	PULM. 2ND SOUND		
1.	6	M	normal	no	no	yes	no	2	120-70	no	yes	5	absent	Pulmonary stenosis	c.a.
2.	8	F	delay	yes (18 months)	no	no	yes	2	100-70	no	yes	5	weak	Trilogy of Fallot	c.a.i.
3.	9	F	delay	yes (18 months)	no	no	yes	1	90-50	no	yes	5	weak	Pulmonary stenosis, left vena cava drain- ing into left auricle	c.a.
4.	10	M	normal	yes (12 months)	yes	no	no	2	100-65	no	yes	5	normal	Pulmonary stenosis	c.a.i.
5.	32	F	normal	no	no	no	no	2	180-110	no	yes	5	weak	Pulmonary stenosis, systemic hyper- tension	c.
6.	9	F	delay	yes (36 months)	no	no	no	4	115-65	yes	yes	4	absent	Pulmonary stenosis	c.n.
7.	19	M	normal	no	no	yes	yes	1	115-60	no	yes	5	weak	Pulmonary stenosis, partial drainage of pulmonary veins into right auricle	c.a.
8.	7	M	delay	yes (12 months)	no	yes	no	2	100-60	no	yes	5	normal	Trilogy of Fallot	c.a.i.
9.	2	M	normal	no	no	no	no	1	—	no	yes	4	weak	Trilogy of Fallot	c.a.
10.	18	M	delay	yes (48 months)	no	no	no	3	150-80	yes	yes	5	weak	Trilogy of Fallot	c.
11.	10	F	normal	no	no	no	no	2	110-70	no	yes	5	weak	Trilogy of Fallot	c.i.
12.	6	F	normal	yes (12 months)	yes	no	no	3	90-60	no	yes	4	absent	Trilogy of Fallot	c.i.n.
13.	2	M	normal	no	no	no	no	1	80-50	no	yes	5	absent	Pulmonary stenosis	—
14.	44	F	normal	yes (38 years)	no	yes	no	4	145-75	yes	yes	5	absent	Pulmonary stenosis	c.i.
15.	42	F	normal	no	no	no	no	2	140-65	no	yes	4	absent	Pulmonary stenosis	—

F. C. = Functional capacity, H. F. = Heart failure, S. M. = Systolic murmur, c. = catheterization, a. = angiocardiology, i. = valvulotomy, and n. = necropsy.

Functional capacity: The functional capacity was good in the majority of the cases. Eleven patients were in Groups 1 and 2. Among them, there existed six cases of pure pulmonary stenosis; four patients with patent foramen (two with cyanosis). The other patient had a pulmonary stenosis with anomalous draining of the left vena cava into the left auricle.

We have found four cases of markedly diminished functional capacity. Two belonged to Group 3. They were cases of venous-arterial shunt and cyanosis. The two remaining belonged to Group 4, and they were pure pulmonary stenosis, both with cardiac failure. In one of them the stenosis was very severe, as the autopsy demonstrated, and the other was the oldest patient (44 years of age).

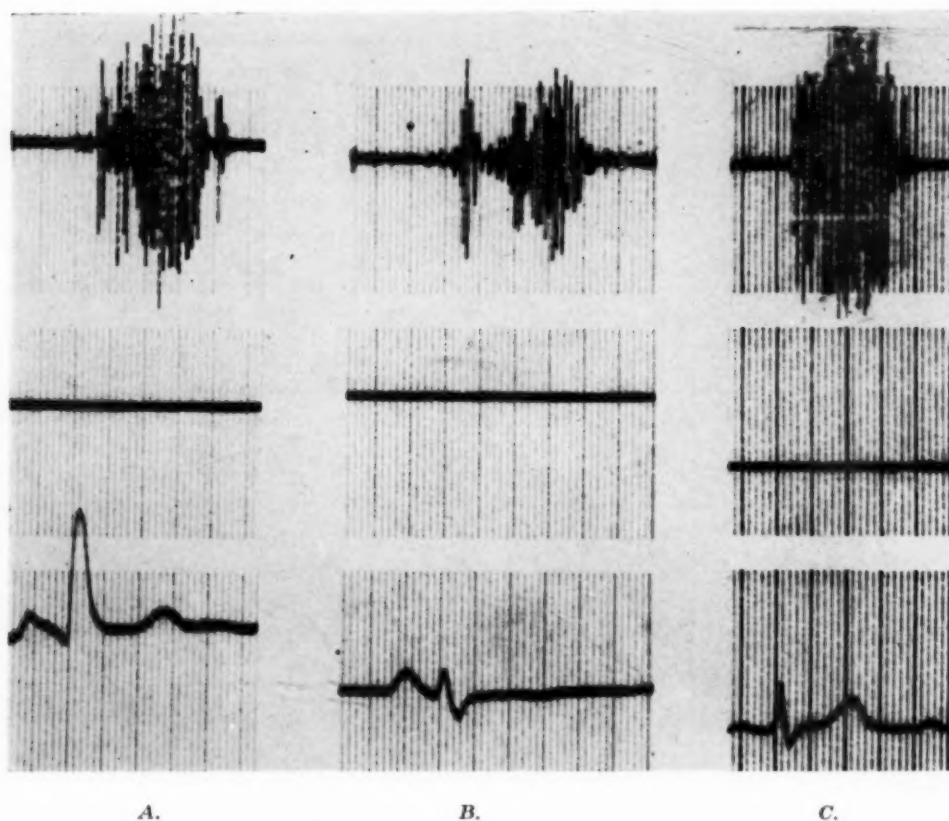


Fig. 1.—Simultaneous phonocardiographic and ECG recordings in (A) Case 5, (B) Case 14, and (C) Case 1.

Cardiac failure: Cardiac failure was present in three cases: two of isolated pulmonary stenosis that are the two belonging to Group 4 of the functional classification, and another case of severe pulmonary stenosis, patent foramen, cyanosis, and considerable cardiac enlargement.

Cardiac examination: All our cases presented a rough systolic murmur of a marked intensity (Types 4 and 5 of the classification of Levine), always accompanied with a thrill in the pulmonary area (Fig. 1); the point of maximum intensity shifting from the left infraclavicular to the third left intercostal space. This murmur was also audible with variable intensity over the entire precordial region and in the back.

The characteristics of the second pulmonic sound are particularly interesting. In none of the cases did it appear increased or split, and only in two cases was it considered normal. In seven cases it was very faint, and in six it was practically inaudible. In some cases we have observed that the second sound, which was perceived at the level of the third left intercostal space, diminished toward the infraclavicular zone, where it completely disappeared, obscured by

the murmur. Probably this is due to the fact that it is the aortic component of the second sound that is heard in the third left intercostal space and cannot be heard further up, owing to the pulmonic murmur.

The peculiar characteristics of the systolic murmur in crescendo, together with the diminution or the absence of the second sound, give the impression that it lengthens itself as far as the beginning of diastole, thus giving a very typical character to the auscultation of this valvulopathy. In fact, what happens is that the right ventricular systole is delayed in relation to the left, owing to the pulmonary stenosis. This leads to an asynchronism in the closure of the pulmonary and aortic valves. This is not perceived on auscultation, because the pulmonary component is so weak that it is hardly audible, but can be easily recorded in a phonocardiographic tracing (Fig. 2).

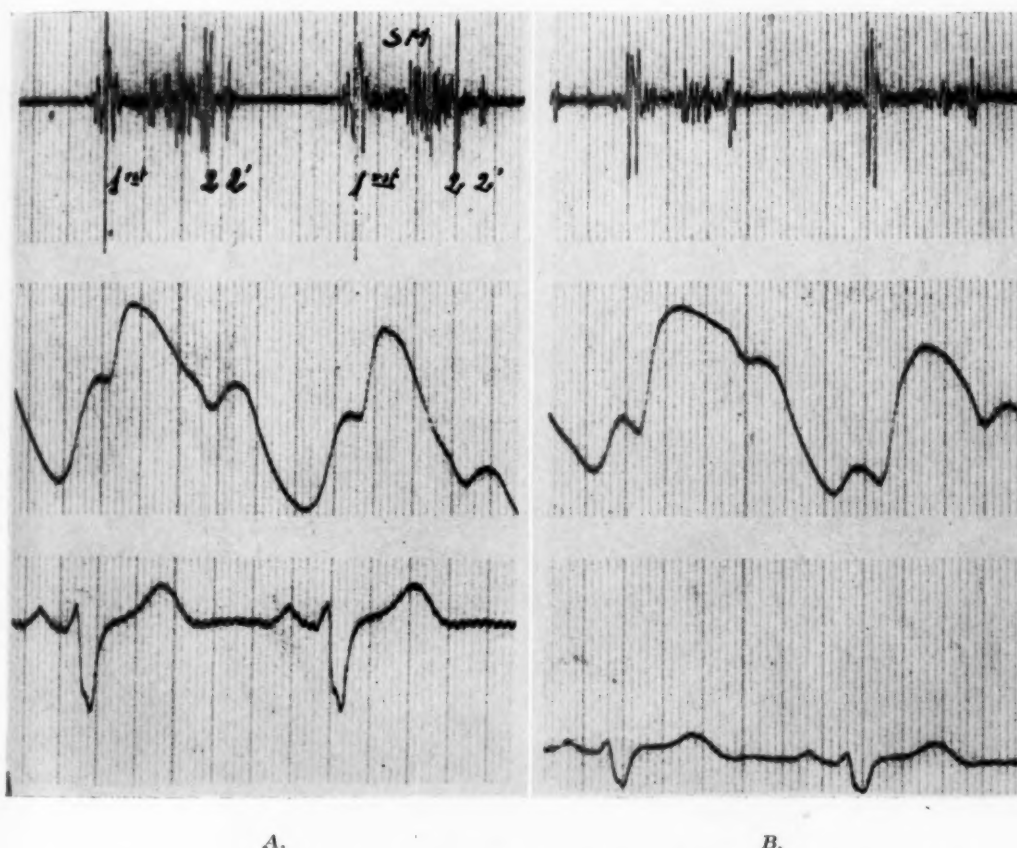


Fig. 2.—Simultaneous recordings of phonocardiogram, carotid arteriogram, and ECG in Case 15. A, Pulmonary area: 2, aortic component of the second sound; 2', pulmonary component. B, Aortic area.

Radiologic.—Table II. The radiologic finding of the greatest diagnostic value is the poststenotic dilatation of the main trunk of the pulmonary artery (Fig. 3), which continues to the prominence of the middle arch. We have ascertained it more or less in all the cases except one. In this, the poststenotic dilatation of the main trunk of the pulmonary artery was verified in the angiocardigram, which demonstrated the central position of the pulmonary artery which, together with the existence of the left vena cava, rendered its radiologic identification difficult.

The prominence of this middle arch is accompanied by hyperpulsatibility. This was more manifest in the pure stenoses. This hyperpulsatibility in some cases reached as far as the two branches of the pulmonary artery, and in various occasions, only one of them: generally the left

one. Different from what occurs in atrial septal defects, the hyperpulsatility did not continue any further, contrasting with the distal brightness of the lung fields.

The cardiac enlargement was slight in six cases, moderate in five, and marked in four, and it was done in detriment to the right cavities and middle arch. The maximum cardiomegaly observed corresponded to a marked pulmonary stenosis with both septa closed (Fig. 4).

Fig. 3.

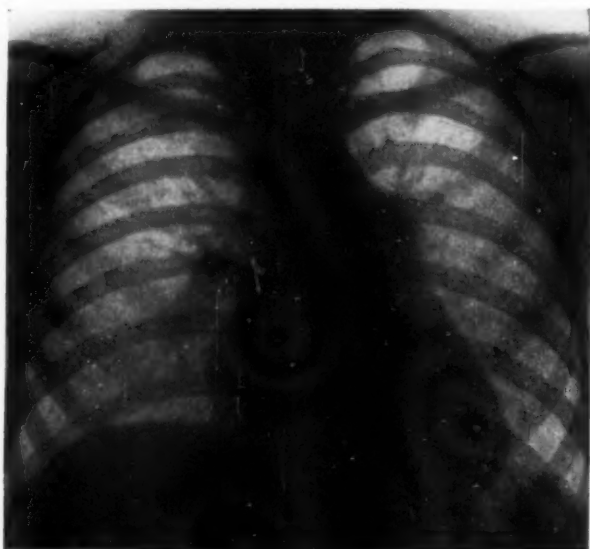


Fig. 4.

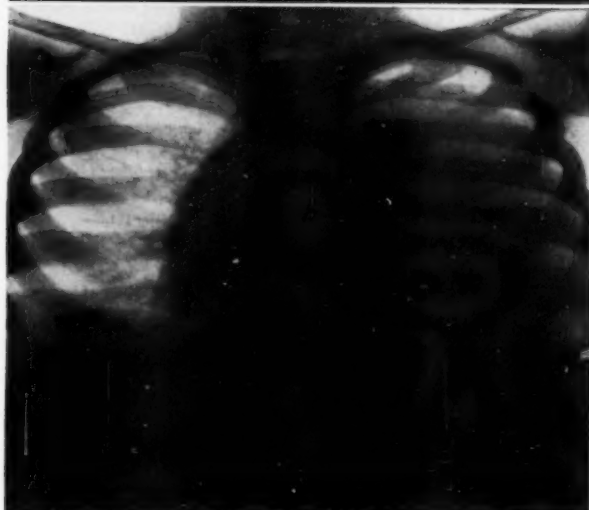


Fig. 3.—Poststrictural dilatation of the pulmonary artery.
Fig. 4.—Unusual cardiac enlargement in Case 5.

The observation of the lung fields is an important clue for the diagnosis. In all except one they appeared vascularized to a small degree. Though the grade of transparency could be considered as normal, the contrast that it presented with the prominence and the hyperpulsatility of the middle arch gave the sensation of hyperclearness, which was real only in one of the cases. The only case in which the pulmonary vascularization appeared somewhat increased was the one in which, besides the pulmonary stenosis, there existed an arteriovenous shunt due to a partial draining of the pulmonary veins into the right auricle.

TABLE II. RADIOLOGIC DATA

	CARDIAC ENLARGEMENT	PROMINENT PULMONIC CONUS	HYPERPULSATIBILITY OF THE MAIN PUL- MONARY TRUNK	LUNG FIELDS
1.	+	++++	yes	Clear
2.	+	++	yes	Clear
3.	+	--	yes	Clear
4.	++	++	yes	Clear
5.	++	++++	yes	Clear
6.	+++++	++++	no	Hyperclearness
7.	+	++	yes	Clear
8.	++	++	yes	Clear
9.	+++	++	yes	Clear
10.	+++	+++	yes	Clear
11.	++	+++	yes	Clear
12.	+	+	yes	Clear
13.	+	+++	yes	Clear
14.	+++	+++	yes	Clear
15.	++	+++	yes	Clear

Electrocardiographic.—Table III. With the exception of one case of auricular fibrillation, the altitude of the P wave was measured in Lead II. In two cases, their height was 4 mm.; in four, 3 mm.; in six, 2 mm.; and in two cases only, it was less than 2 mm. In the cases in which the P wave was of increased voltage the duration was normal.

The electrical axis of the QRS was deviated to the right in all the cases except in Case 15, which happened to be 60 degrees and was in a woman in her eighth month of pregnancy. The right axis deviation in the remaining cases was 90 degrees minimum. In one case, there existed an axis hyperdeviation at -150 degrees.

We have found a typical pattern of right ventricular hypertrophy in thirteen cases; in two of them, it was accompanied with a right bundle branch block. In another case, there existed only an incomplete right bundle branch block. The only case without the right hypertrophy

TABLE III. ELECTROCARDIOGRAPHIC DATA

	P _{II} WAVE HEIGHT	QRS AXIS	RIGHT VENTRICULAR HYPERTROPHY PATTERN				DIAGNOSIS
			AS FAR AS:	QRS	ACTI- VATION TIME	T WAVE	
1.	1.5	+102	V ₃ D	R	0.03	—	R.V.H.
2.	3	+ 90	V ₁ -V ₂	Rs	0.04	—	R.V.H.
3.	3	+108	V ₃ D	qR	0.03	—	R.V.H.
4.	2	+128	V ₃ D-V ₁	R	0.04	—	R.V.H.
5.	2	+114	V ₁ -V ₂	R	0.04	—	R.V.H.
6.	4	+ 90	V ₁ -V ₅	rsR's	0.06	—	R.V.H.-R.B.B.B.
7.	2	+ 90	V ₁ -V ₃	rS	0.04	+	I.R.B.B.B.
8.	2	+108	V ₆ D-V ₄ D	R	0.05	+	R.V.H.
9.	2	+162	V ₃ D	R	0.03	—	R.V.H.
10.	4	-150	V ₃ D-V ₂	Rs	0.04	—	R.V.H.
11.	2	+ 90	V ₁	R	0.03	—	R.V.H.
12.	3	+125	V ₁ -V ₄	Rs	0.04	—	R.V.H.
13.	1	+101	V ₃ D-V ₁	rsR'	0.04	+	R.V.H.-I.R.B.B.B.
14.	—	+122	V ₁ -V ₃	R	0.04	—	R.V.H.-A.F.
15.	3	+ 60	—	rS	0.02	+	—

R.V.H. = Right ventricular hypertrophy, I.R.B.B.B. = Incomplete right bundle branch block, and A.F. = Auricular fibrillation.

pattern or the right bundle branch block was Case 15, in which the position changes of the heart, on account of the patient's pregnancy, suggested the possibility that the image was not recorded in the usual leads.

The right ventricular hypertrophy pattern appeared only in one or more right extreme precordial leads in four cases (Fig. 5), the patients, ages being between 2 and 9 years, extended up to V_1 lead in three cases, and in six there appeared right hypertrophy pattern in "barrage" that, in one case, even reached the V_5 lead (Fig. 6); the ages of these patients was between 6 and 44 years, with an average of 19. The delay in the right ventricular activation time was 0.03 second or more in all the cases but one. The T was negative in the leads showing the pattern of right ventricular hypertrophy in eleven of the thirteen cases.

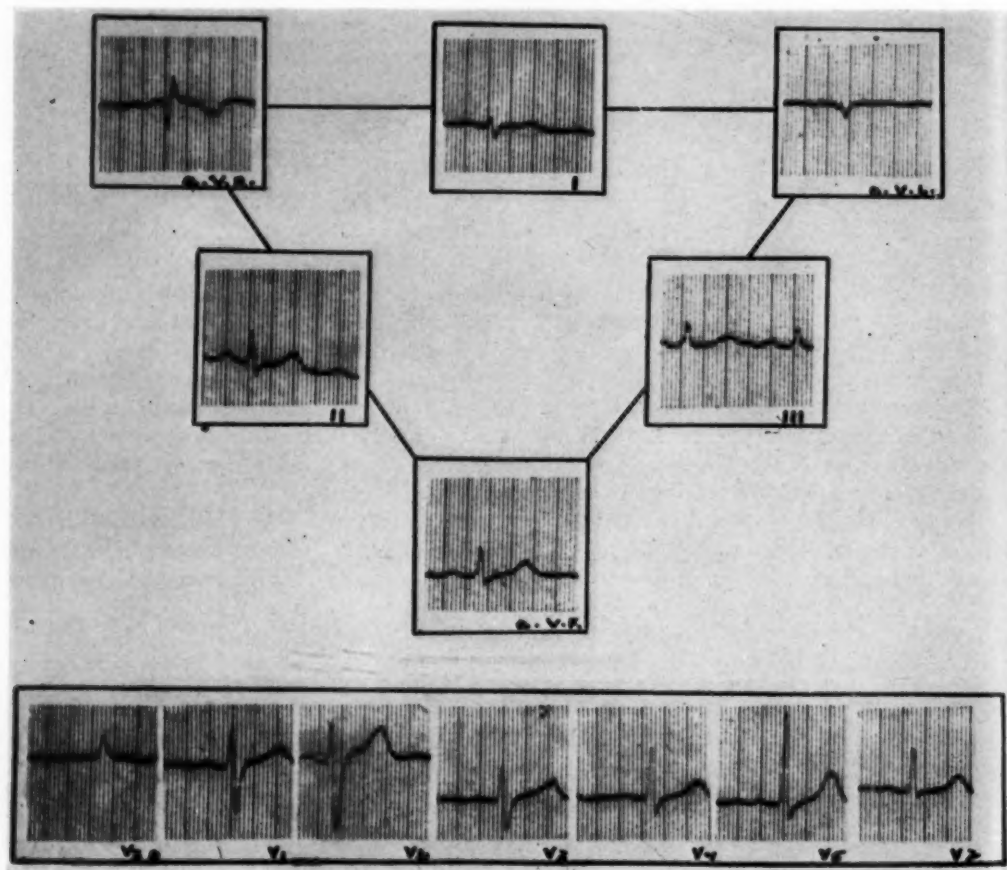


Fig. 5.—Moderate right ventricular hypertrophy pattern in Case 1.

Ballistocardiographic.—Table IV. In seven cases, a ballistocardiographic tracing was performed with an electromagnetic apparatus of the Dock type. In Table IV are listed the ballistocardiographic data. The tracing was altered in two cases, it was normal in three, and in the other two there were only alterations during the expiration phase. The pathologic alterations referred especially to J and K waves, consisting of a lesser height of the J, and broadening of the K wave (Fig. 7).

Hemodynamic.—Table V. From the group of eleven cases in which the cardiac catheterization could be carried through, the pulmonary artery could be catheterized in seven of them, verifying the pressure gradient between the right ventricle and the pulmonary artery. In all these instances, the pulmonary artery hypotension was verified and it oscillated from 7 to 20 mm.

Hg for the systolic pressure. In all the cases, a marked systolic hypertension appeared in the right ventricle, which oscillated between 70 and 140 mm. (Fig. 8).

In Case 3, the catheterization proved the existence of a persistent superior vena cava draining into the left auricle (Fig. 9); for this reason, it was not possible to record the pressures in the pulmonary artery and in the right ventricle.

In Case 7, the catheterization proved the existence of a partial drainage of the pulmonary veins into the right auricle (Fig. 10).

Generally, the withdrawal of the catheter from the pulmonary artery to the right ventricle showed an abrupt change in the pressure at the level of the pulmonary valve. In only one case there appeared, in the pressure curve, an intermediate pressure zone suggestive of an infundibular chamber.

In some instances, when the catheter tip was close to the valve, there appeared a negativity in the pulmonary pressure tracing, due to a phenomenon of Venturi.

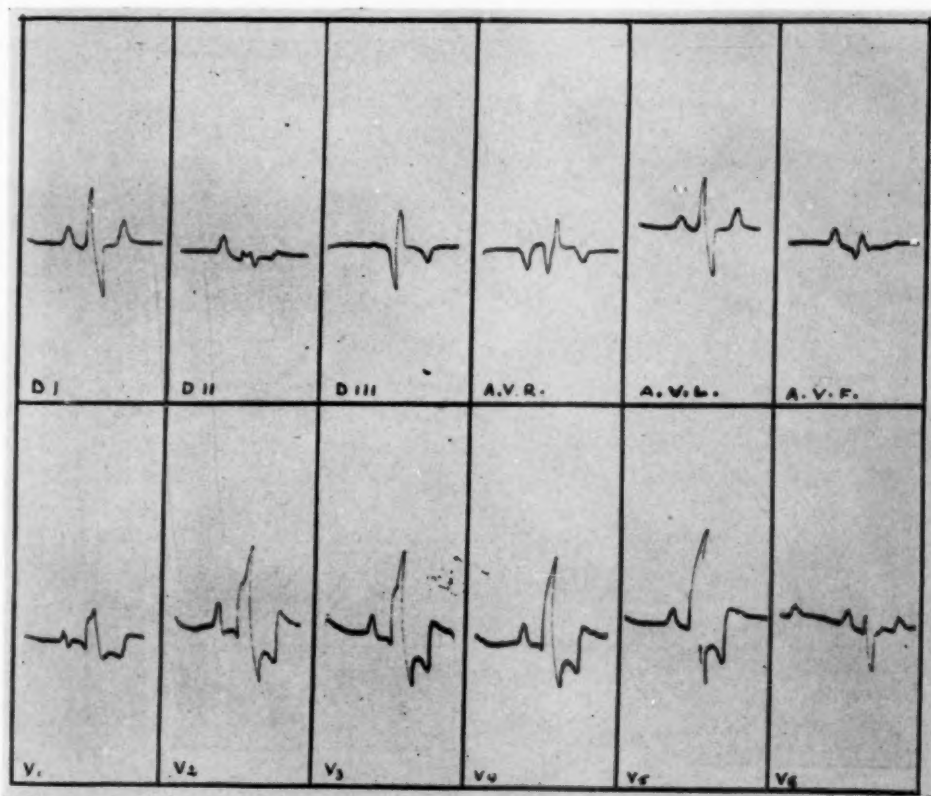


Fig. 6.—Severe right auricular and ventricular hypertrophy with ST-T changes as far as V_5 precordial lead ("Barrage type").

The right ventricular pressure tracing was very characteristic in all the instances, adopting the form of an isosceles triangle as a result of the disappearance of the ejection plateau and the lengthening of the ventricular tension phase. The tracings of this type are characteristic of pulmonary stenosis with closed ventricular septum, and they are clearly differentiated from those of the tetralogy of Fallot. Another differential characteristic is the inequality in the systolic pressure between the right ventricle and the aorta, the former sometimes keeping below and other times, above it.

In four cases the catheter passed from the right auricle to the left, rendering evidence of the patency of the foramen ovale or the existence of a true atrial septal defect (Fig. 11). In the majority of the cases, the attainment of this maneuver was purposely sought. In Case 6, the

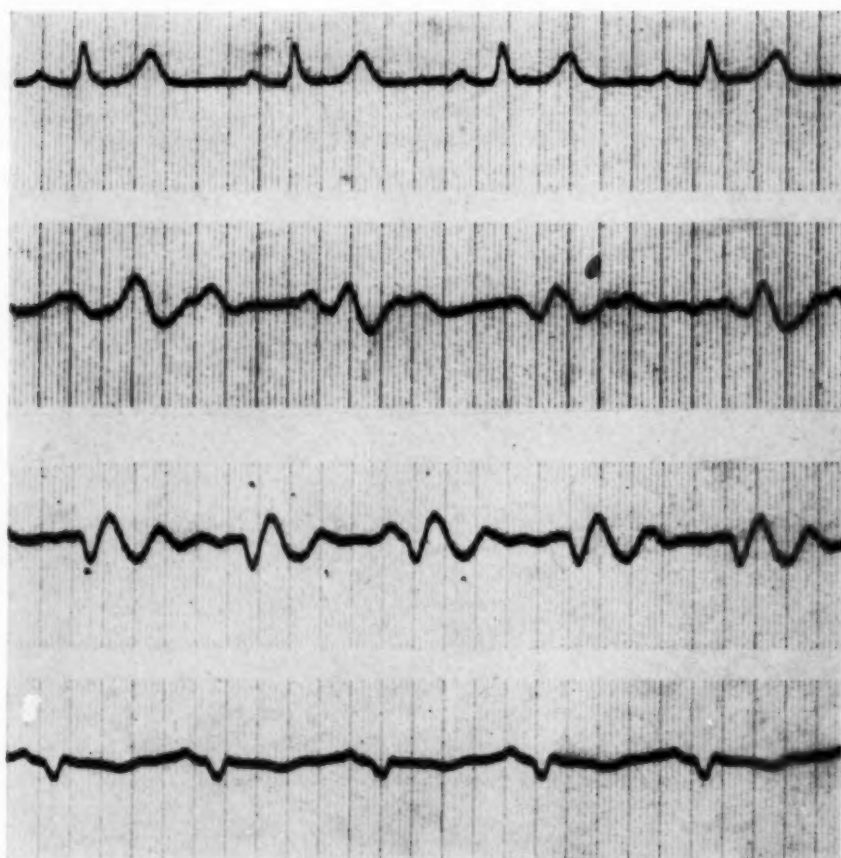


Fig. 7.—Simultaneous ECG and BCG tracings in (A) Case 15 and (B) Case 3.

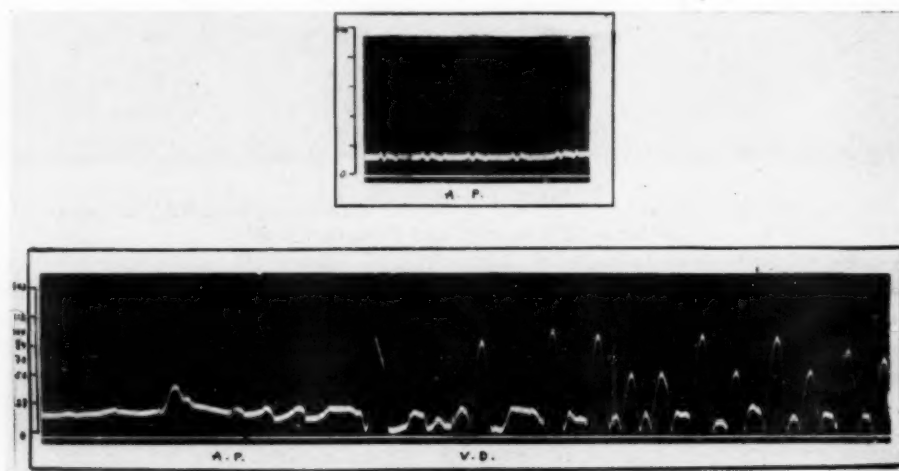


Fig. 8.—Pressure tracing from the pulmonary artery to the right ventricle in Case 11.

catheter, in spite of repeated maneuvers, did not pass from the right auricle where there was a hypertension (superior to 30 mm.). In this instance, the right auricle was enormously dilated and the atrial septum was entirely closed.

In Table V, there appear the corresponding values of the pulmonary and systemic flows in the cases that could be calculated. In Case 4, the values appear somewhat high, probably because the patient did not happen to be in basal conditions. In Case 7, the pulmonary flow appears increased, owing to an arteriovenous shunt that was produced through an anomalous pulmonary drainage into the right auricle. In Case 12, there existed a venous-arterial shunt at the auricular level, with diminution in the pulmonary flow. In three other instances of venous-arterial shunt at the same level, it was demonstrated by other facts, but we have no sufficient oxymetric data for the calculations.

The pulmonary valve area was calculated by means of Gorlin's formula in six cases, giving values that oscillated between 0.1 and 0.5 cm.². The valvular resistance, in accordance with Dow, in the same cases gave values between 481 and 3867 dynes/sec./cm.⁵.

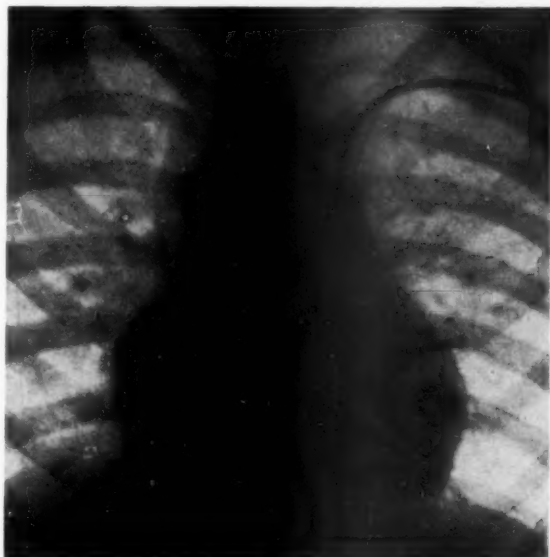


Fig. 9.—Catheterization of persistent left superior vena cava draining into the left atrium. Catheter tip in a left pulmonary vein (Case 3).

Angiocardiographic.—Table VI. In seven cases, an angiocardiographic exploration was performed with the following results: In all of them, the evacuation of the right ventricle was delayed, and there was clearly visualized the poststenotic dilatation of the main trunk of the pulmonary artery, appearing in various instances as a typical image in "racket" (Figs. 12 and 13). In three cases there was ascertained an early opacification of the left auricle and of the aorta (Fig. 14). Different from what happens in the tetralogy, the aortic opacification did not appear simultaneously with the pulmonic one, but in the following exposure, its intensity was less apparent. Except for Case 7, which presented an arteriovenous shunt, the pulmonary markings appeared poorly in all of the cases.

DISCUSSION

In accordance with the experience of previous authors, pulmonary stenosis with closed ventricular septum presents itself with relative frequency. Thus, we have been able to gather, since the year of 1949, a total of fifteen cases in which the diagnosis has been possible to establish during life. The presence of

a rough systolic murmur in the pulmonary area accompanied by a thrill; with the second pulmonary sound being absent, weak, and seldom normal; and with a poststenotic dilatation of the main trunk of the pulmonary artery at x-ray examination in a patient with or without cyanosis, give us the clue for the clinical diagnosis.



Fig. 10.

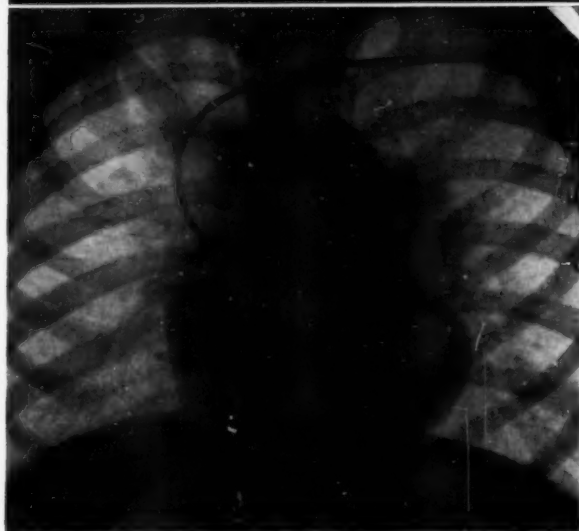


Fig. 11.

Fig. 10.—Catheterization of an aberrant pulmonary vein draining into the right atrium in Case 7.
Fig. 11.—Catheterization of the left atrium through a patent foramen ovale in Case 11.

The cyanosis that may be present in this malformation can be either of the central or the peripheral types. If the cyanosis is of the central type, it is due to a patent foramen ovale, or, more rarely, to a true atrial septal defect,¹¹ provided that there does not exist any other anomaly apt to give a venous-arterial shunt. In one of our cases it was due to a persistent left vena cava draining into the left

auricle. The absence of cyanosis, otherwise, does not presuppose anything about the condition of the atrial septum.

The cyanosis that may appear when the atrial septum remains completely closed is of the peripheral type and coincides with the cardiac failure.



Fig. 12.



Fig. 13.

Fig. 12.—Angiocardiography in Case 3.

Fig. 13.—Angiocardiography in Case 1.

The cyanosis in this malformation is considered as being of late appearance.^{1,5,8} However, if the stenosis is severe it may appear early or even earlier than in the tetralogy of Fallot. Thus, in three of our cases it appeared within the first year of age. Johnson and Johnson¹² and Wood⁶ have seen its appearance even at birth. According to our own experience, the rarity of the squatting position and of the syncopal attacks permits, in these cases, differentiation from Fallot's tetralogy.

The exercise tolerance depends almost exclusively on the severity of the stenosis. One of our patients died at 9 years of age because of cardiac failure. In contrast, we have found two patients, 42 and 44 years of age, one of them with perfect tolerance. In the literature there also appear several patients who have reached old age;^{14,15} one of them reached 78 years.¹³ Among our cases the good functional capacity of the majority of our patients has been evident, which, besides being related to the degree of stenosis, ought also to be related to age, since the mechanical conflict represented by the stenosis increases along with the development of the individual.

In two-thirds of our cases, the bodily development was within normal limits. There existed a clear relation between the development delay and the presence of a venous-arterial shunt, coinciding with what was observed by Sobin and associates.²

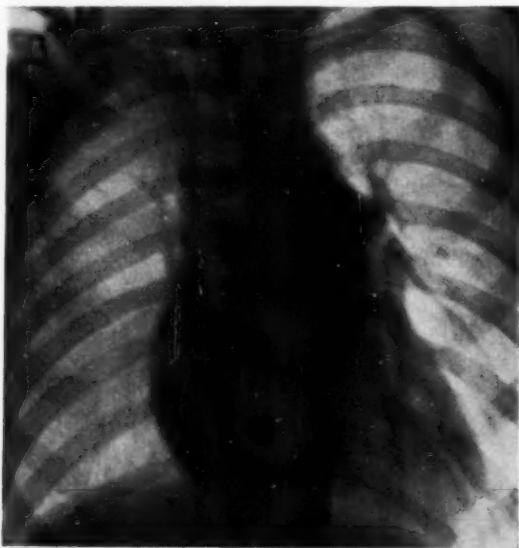


Fig. 14.—Early filling of the left atrium and aorta in Case 2.

The presence of right cardiac insufficiency, opposite to the tetralogy of Fallot is a frequent event and is attested by the frequency of the hepatic cirrhosis found at autopsy in some cases.¹¹ Its intensity reaches its maximum when both septa are closed, the presence of a gross ascites being possible, simulating constrictive pericarditis but with a larger heart, as in our Case 6.

One of the most characteristic findings of the physical examination is the constancy with which the systolic pulmonary murmur is accompanied by thrill. The murmur's characteristics confer on it a peculiar aspect that has induced Donzelot to give to it the qualification of "stenosis murmur."⁸ With this peculiar aspect contributes either the disappearance or the diminution of the second pulmonary sound, in addition to the delay of the right ventricular systole, which gives the acoustic impression that the murmur lengthens out somewhat into diastole. Sobin² sustains the opinion that some of the diastolic murmurs which have been described in some of these cases must be imputed to

the final phase of the systolic murmur and that the lack of the second pulmonary sound renders the identification difficult.

Radiologically, the most important finding consists in the poststenotic dilatation of the main trunk of the pulmonary artery that contrasts with the

TABLE IV. BALLISTOCARDIOGRAPHIC DATA

	TYPE	HEIGHTS			INTERVALS			MORPHOLOGY OF WAVES			DIASTOLIC WAVES
		I-J	J-K	Q-I	Q-J	Q-K	I-J/I-N	H AND I	J	K	
1.	3	4	10	0.14	0.21	0.30	4	n.	low voltage	widened	absence N.
3.	1	6	6	0.14	0.19	0.29	2	n.	low voltage	widened	—
5.	1	6	8	0.14	0.17	0.24	1.7	n.	low voltage	widened	—
7.	2	6	7	0.16	0.24	0.32	6	n.	low voltage	widened	absence N.—wide L.
8.	4	—	—	—	—	—	—	Waves without identification			—
14.	4	4	4	0.12	0.20	0.30	—	absence	low voltage	—	without identification
15.	2	4	11	0.18	0.21	0.28	1.3	n.	low voltage	widened	—

n. = normal.

TABLE V. HEMODYNAMIC DATA

	PRESSURES				FLOWS		PULMONARY AREA	PULMONARY VALVULAR RESISTANCE
	PULMONARY ARTERY		RIGHT VENTRICLE		SYSTEMIC	PULMONARY		
	S	D	S	D				
1.	7	2	79	1	3020	3020	0.5	1343
2.	—	—	70	6	—	—	—	—
4.	13	6	78	13	6300	6300	0.3	559
5.	14	10	120	14	3520	3520	0.3	1588
7.	8	2	95	2	5200	8900	0.5	481
9.	—	—	93	5	—	—	—	—
10.	20	10	130	3	—	2060	0.1	3820
11.	10	5	99	8	—	—	—	—
12.	14	1	140	5	3800	1900	0.1	3867

TABLE VI. ANGIOCARDIOGRAPHIC DATA

	L.A. EARLY OPACIFICATION	R.V. DELAYED EVACUATION	POSTSTRICTURAL DILATATION	EARLY AORTA OPACIFICATION
1.	no	yes	yes	no
2.	yes	yes	yes	yes
3.	no	yes	yes	no
4.	no	yes	yes	no
7.	no	yes	yes	no
8.	yes	yes	yes	yes
9.	yes	yes	yes	yes

normal or somewhat diminished vascularization of the lung fields. The dilatation of the pulmonic trunk is generally accompanied by its increased pulsation (Soulié and associates⁴). In other instances, the hyperpulsatibility is due to the coexistence of an atrial septal defect that permits an arteriovenous shunt, even in spite of the pulmonary stenosis.^{16,17} In these cases, the hyperpulsatibility may reach as far as the middle branches of the pulmonary artery, and the lung fields may appear somewhat vascularized, as in one of our cases which we do not include in this report.

The cardiac size may present various grades of enlargement, though generally it is more manifested than in the tetralogy.

The electrocardiogram is of a great value for the diagnosis. When the pulmonary stenosis is slight and the patient is of an early age, the patterns of right ventricular hypertrophy may be lacking⁵; however, in our own cases, we have seen them to appear in the extreme right precordial leads. Donzelot and associates¹⁸ have described, as being typical in this malformation, the pattern of right ventricular hypertrophy of the "barrage" type, which consists in the extension of the hypertrophy "pattern" up to the V_2 lead, it being possible to reach even the V_5 and the V_6 leads, accompanied with manifested inversion of the T waves. This electrocardiographic pattern has been frequent in our cases, being related to the degree of pressure of the right ventricle,¹⁹ which depends on the degree of stenosis and the age of the patient. In some cases we have seen right bundle branch block accompanying the hypertrophy pattern. In one case in which the right bundle branch block was pure, it could be explained by reason of the coexistence of a partial drainage of the pulmonary veins into the right auricle.

The P-wave modifications are characteristic; they were present in twelve of the fifteen cases, they consist in the increased voltage of the P wave, and they are seen especially in Lead II. These modifications indicate right auricular strain.

The cardiac catheterization enables us to obtain findings that leads to the diagnostic certitude of pulmonary stenosis, by verification of the pressure gradient between the pulmonary artery and the right ventricle. The pressure change is generally abrupt, and the radioscopic control ascertains that it takes place at the valvular level. In one case only we have been able to verify the existence of an intermediate pressure curve between that of the pulmonary artery and the right ventricle, analogous to those observed by Kirklin and associates⁹ in cases of double valvular and infundibular stenosis. This type of stenosis, being frequent in the tetralogy of Fallot, is rarely seen in simple pulmonary stenosis, and in this sense our experience coincides with that of Campbell.¹ On the contrary, Larson and associates²⁰ sustain the opinion that many of the isolated cases of pulmonary stenosis of the moderate type are of the infundibular pattern, though they do not bring definitive proof to corroborate this.

Bouchard and Cornu²¹ have recently carried out a close differential study of the pressure curves in pulmonary stenosis and in the tetralogy of Fallot, calling attention to the presence of the curves of Venturi in the first type. These curves are characterized by the appearance of a systolic negativity in the pulmo-

nary pressure tracings, which become more evident when the catheter tip is located right upon and close to the valvular orifice; this is due to the great speed that the blood flow acquires when passing through the stenosed orifice, establishing a vacuum through aspiration when running away from the catheter point. As it is confirmed by Sobin and associates,² these curves are systematically verified in this type of stenosis if the catheter's withdrawal is carried out in a careful manner, and they mention the possibility of confusing these curves with those that may be obtained when there exists an infundibular chamber. At any rate, in this last case the diastolic pressure is never less than 0, and the systolic level is uniform in the whole chamber, while the phenomenon of Venturi becomes more apparent at the time when we come near the valve.

The morphologic aspect of the ventricular pressure curve also differs whether or not there exists an overriding aorta. In the first instance, the morphology is similar in both ventricles,²¹ while in the case of pulmonary stenosis with closed ventricular septum the isometric tension time lengthens and the ejection plateau disappears, the curve adopting an acuminate aspect which we have verified in nearly all the cases. Besides these characteristics the systolic level between the right and the left ventricles which equalize themselves in the tetralogy, by consequence of the aortic overriding, are different in the case of pulmonary stenosis, in which the right ventricular systolic pressure might markedly overcome the aortic pressure in the cases of severe stenosis.²² Among our own cases this has been of little frequency, owing to the young ages of the majority of our patients and to the fact that two cases presenting a high right ventricular systolic pressure also presented systemic hypertension. When the pulmonary stenosis is moderate, the right ventricular pressure situates itself at a lower level than the aortic pressure, as emphasized by Soulié and associates.⁴

In the absence of a venous-arterial shunt, the catheterization of the left auricle allowed confirmation of a patent foramen ovale. The existence of a true atrial septal defect may only be assured when an arteriovenous shunt is verified, which coexistence with a pulmonary stenosis has been demonstrated by Broadbent and associates¹⁶ and Rudolph and colleagues,¹⁷ inasmuch as the sole patency of the foramen ovale only permits the right-to-left shunt. In these instances the oxymetry proves the arterialization of the right auricle, notwithstanding that this finding may also be due to the presence of an anomalous drainage of the pulmonary veins, as we had the opportunity of verifying in our Case 7.

The angiocardigraphic data have been very typical in all the cases, demonstrating in an evident manner the poststenotic dilatation of the main trunk of the pulmonary artery and the delayed evacuation of the right ventricle, the pulmonary opacification persisting till the last plates. If the foramen ovale is patent, there may appear early opacification of the left auricle and the aorta, the latter being within the possibility of appearing opacified without opacification of the left ventricle, as if, making use of Kreutzer's expression that the contrast medium was "aspired" by the aorta when crossing the mitral valve.⁷ This early opacification of the aorta, different from what occurs in the biventricular aorta cases, is little delayed, always being accompanied with a left auricular opacification, and it is less intense than that of the pulmonary artery. In these cases, too, there is observed a good tardive levogram that never appears in the tetralogy, except in the case in which the aortic overriding is minimum.

Sellors²³ and Brock²⁴ demonstrated, in 1948, the possibility of these patients' recovery by means of the transventricular direct valvulotomy; and after that time, with the observation of a greater number of cases, it has been found that not all of them require a surgical treatment, inasmuch as if the stenosis is moderate it is possible to have a good functional capacity. This the reason for the necessity of some selective criteria to indicate operation. To some authors, the operation is indicated when the systolic pressure of the right ventricle surpasses the systemic pressure.⁴ Campbell judges that it is better to be guided by a fixed level, in his opinion, of 100 mm. Hg, which point of view we hold, as in our cases there were two with systemic hypertension for which the application of the first criterion would have been equivocal. In the electrical data, the presence of an electrocardiographic pattern in "barrage" constitutes a good criterion for the indication of surgery, which will also be evident whenever the cardiopathy is tolerated poorly.

SUMMARY

The authors have selected fifteen cases of pulmonary stenosis with closed ventricular septum; in six patients could be demonstrated the presence of a patent foramen ovale or a true atrial septal defect; in two other cases there existed an anomaly of the venous return. The diagnosis was verified in two cases by autopsy, in five by surgical intervention, in twelve by cardiac catheterization, and in seven by angiocardiology.

The most important clinical data for the diagnosis were the presence of loud systolic murmur accompanied by a thrill and the diminution or the absence of the second pulmonary sound. The most important radiologic finding consists in the poststenotic dilatation of the main trunk of the pulmonary artery, with clear or normal lung fields, the cardiac enlargement varying from case to case, in relation to age and the degree of stenosis.

Electrocardiographically there appeared some signs of right ventricular hypertrophy in thirteen cases, and in six cases the pattern extended further than the V_1 lead.

From the hemodynamic point of view the most outstanding finding was the pressure gradient between the pulmonary artery and the right ventricle; the change in pressure was found at the valvular level, except one case in which there existed an intermediate pressure zone suggestive of an infundibular chamber. Opposite from the tetralogy of Fallot, the systolic pressure of the right ventricle may be as much above as below the aortic pressure, placing itself above when the stenosis was of a severe degree. Emphasis is placed on the shape of the right intraventricular pressure curve, as well as the appearance of the Venturi curves. The angiocardiology shows poststenotic dilatation of the main trunk of the pulmonary artery, the delayed evacuation of the right cavities, and the early opacification of the left auricle, when the foramen ovale is patent.

Finally, the criteria for the surgical selection of the cases is discussed because the patients with only a slight pulmonary stenosis do not call for surgical treatment.

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ADDENDUM

After the completion of this paper, patient 14 underwent a pulmonary valvotomy successfully. After confirming her pulmonary stenosis by catheterization, the right ventricular systolic pressure was above 140 mm.

UNUSUAL CAUSES OF DEATH AFTER CARDIAC SURGERY

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ALTHOUGH numerous commissurotomies for mitral stenosis have been performed during the past eight years, pathologic reports of cardiac deaths during or shortly following the surgery are few. In this paper are reviewed pathologically some unusual cases observed at the Massachusetts Memorial Hospitals of patients who have died after cardiac operations for mitral or aortic deformities.

In the 1920's commissurotomy was performed in twelve cases of chronic valvular disease of the heart, including mitral stenosis, aortic stenosis, and pulmonary stenosis.¹ Three survived the operation and showed improvement. The others died from bronchopneumonia, shock, or accompanying congenital defects. Following World War II with the development of better anesthesia, experience gained with thoracic battle casualties, and antibiotics, commissurotomies were once again performed. Janton² reported eleven deaths occurring among the first 100 cases from 1948 to 1950. Six of these eleven deaths were attributed to surgically induced mitral insufficiency. Others died from a failure to relieve the mitral stenosis, along with surgical trauma, cerebral embolism before the appendage was routinely ligated at its base, hemorrhage, and shock. In 1951 a mortality rate of 6 per cent was ascribed to operative embolism.³

Glover and associates,⁴ in reviewing 164 of their cases, reported a patient with unsuspected complicating aortic stenosis who died in forward failure following mitral commissurotomy. In 1953, Andrus, Blalock, and Milnor⁵ reported on a patient who died from staphylococcal pericarditis following mitral commissurotomy. In 1954, Effler, Groves, and Sones⁶ reviewed 100 cases of mitral commissurotomy in Cleveland and divided a mortality of 8 per cent into three categories: (1) cerebral embolization, (2) error in technical management, e.g., quinidine toxicity or cardiac tamponade, and (3) the bad risk patient, e.g., severe pulmonary disease. Pender⁷ emphasized anesthesia as a cause of death producing vasodilatation, a fall in blood pressure, and hypoxia in patients with mitral stenosis who had a fixed cardiac output. Larzelere and Bailey^{8,9} considered deaths after aortic commissurotomy with the ventricular approach through decompensated and often flabby muscle to be from ventricular fibrillation, severe bleeding because of the failure of sutures to hold in the peculiarly soft muscle, and an aortic insufficiency inadvertently created.

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Our interest in unexpected causes of death after cardiac operations dates from observing elsewhere a case in which, during mitral commissurotomy, the heart was apparently pressed against an exostosis of a thoracic vertebral body, producing a hematoma of the myocardium and compromising a coronary artery with an associated myocardial infarction at autopsy.

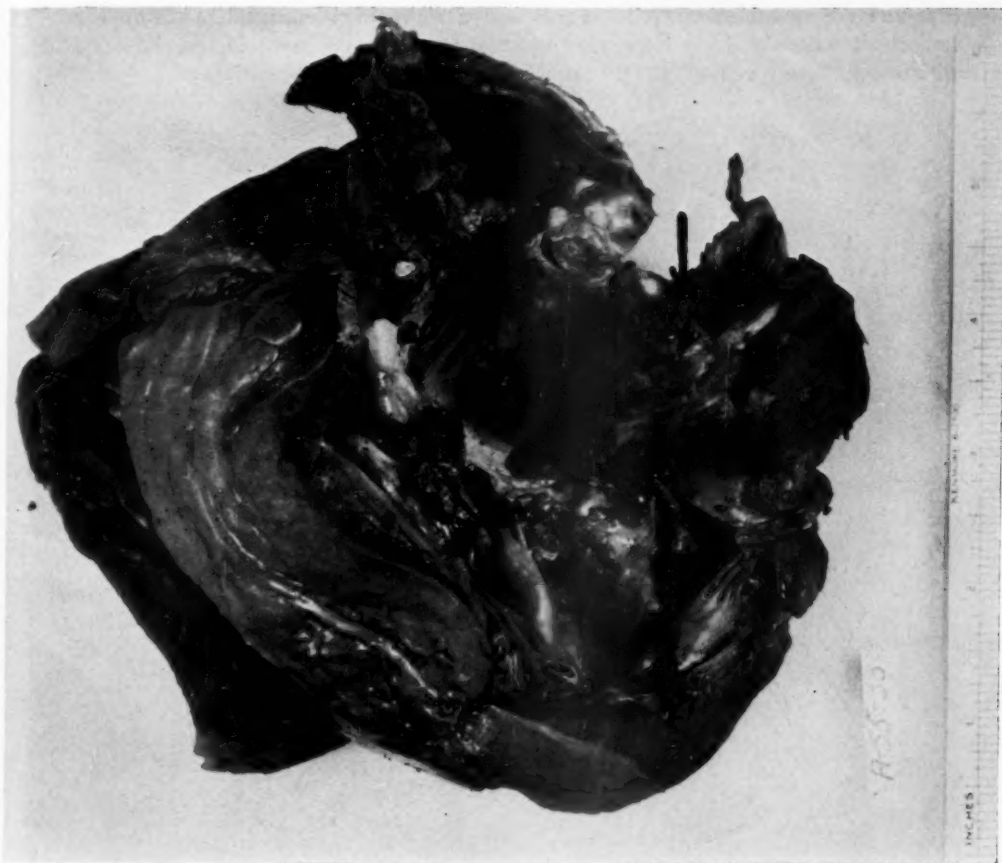


Fig. 1.—Case 1. The left ventricle is shown opened. The left atrium contains a large ball-valve thrombus (arrow).

CASE REPORTS

CASE 1.—(MMH-377626) This 43-year-old, white married nurse with mitral stenosis without a history of rheumatic fever was transferred from the medical service to the thoracic service on March 6, 1955, for a mitral commissurotomy. She had experienced refractory auricular fibrillation and moderate congestive failure for many months. She sustained pulmonary emboli from her leg veins injured in an accident at home in December, 1954, and was admitted to the medical service. Despite heparin therapy, bouts of pleuritic pain necessitated superficial femoral vein ligation. Subsequently a right empyema thoracis developed and was treated with thoracentesis and antibiotics. Cardiac decompensation was controlled. In February, 1955, function studies showed a 33 per cent reduction in pulmonary reserve; however, exercise tolerance was good. Physical examination revealed auricular fibrillation, a palpable diastolic thrill with a Grade 3 diastolic rumble and systolic murmur at the apex. Neck veins were distended and basal râles were present. The major cause of ventilatory insufficiency was believed due to adhesions rather

than mitral stenosis. On March 7, 1955, optimum time for a commissurotomy was believed to have been reached. A laminated thrombus was found occupying the left appendage and was dissected free posteriorly, leaving only enough room to insert a little finger for fracture. The valve was markedly calcified posteriorly. Finger fracture left some regurgitation. The patient became hypotensive and cyanotic, but reacted well from anesthesia. However, three hours later she showed progressive hypotension and cyanosis of the nose and finger tips. She failed to respond to medications and shortly succumbed.

Post-mortem examination (A-55-33) showed a right-sided encapsulated empyema. The left atrium was occupied by a huge, ante-mortem mural thrombus projecting into and almost occluding a pulmonary vein (Fig. 1). Mitral valve admitted an index finger.



Fig. 2.—Case 2. The left ventricle and atrium are exposed. The interauricular septal opening (arrow) is evident.

Comment.—This poor-risk patient's heart and lungs were unable to cope with the surgically produced mitral regurgitation into an auricular cavity occupied by a large thrombus, which was believed to act like a ball valve post-operatively.

CASE 2.—(MMH-378001) This 50-year-old, white married woman was admitted to the Evans Memorial Hospital for a mitral commissurotomy on May 10, 1955. The patient had suffered rheumatic fever at age 13 years, was treated for subacute bacterial endocarditis in September,

1954, at this hospital, and since then suffered severe exertional dyspnea, despite digitalis maintenance. On this, her final admission, she was discovered to have diabetes mellitus which was adjusted with diet and insulin. A Grade 3 diastolic murmur with a Grade 2 systolic murmur were heard at the apex. A Grade 2 systolic murmur was heard over the base. The pulmonic second sound was loud and split. No auricular fibrillation or edema was noted. ECG showed left auricular enlargement and right ventricular hypertrophy. Chest x-ray showed passive congestion of both lungs. Preoperatively the patient was placed on erythromycin therapy. On May 17, 1955, a valvulotomy was performed and the mitral valve was found to be heavily calcified. The orifice was markedly narrowed. A slight regurgitation was questioned as present. The valve was fractured. In closing the pericardium multiple premature beats followed by ventricular tachycardia appeared, and at times no blood pressure was perceptible in the extremities. The patient improved quickly; however, two hours later she went into shock and, despite reopening of the chest and cardiac massage with various medications, she soon expired.

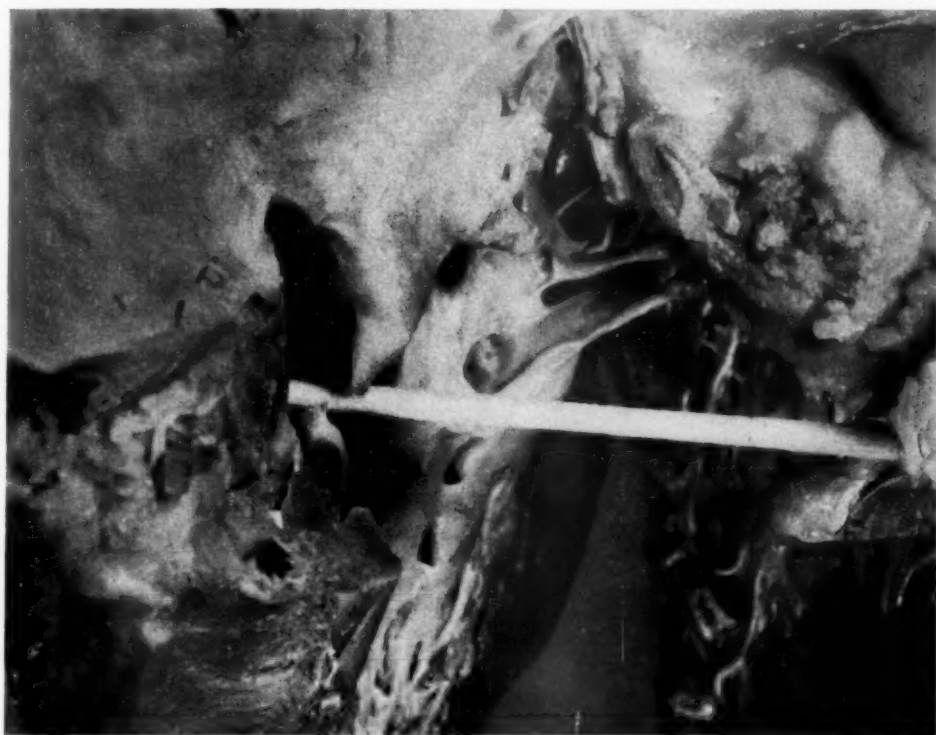


Fig. 3.—Case 3. The slitlike openings in the mitral valve are from the surgical commissurotomy. The chordae tendineae are thickened and a heavily calcified valve cusp is visible.

On post-mortem examination (A-55-57) a patent interauricular septal defect (patent foramen ovale) was found (Fig. 2). The left auricle was not dilated. The mitral valve was calcified with a 0.5 cm. fracture line present. Right ventricle measured 0.2 cm. in thickness.

Comment.—This was an undiagnosed case of Lutembacher's syndrome. Cases with congenital heart defects do not do well with this type of surgery, especially if a regurgitation was surgically produced.

CASE 3.—(MMH-373655) This 52-year-old, white, married, retired man was admitted on May 23, 1954, to the surgical service of MMH for mitral commissurotomy, but because of intractable heart failure was shortly transferred to the medical service for therapy and evaluation before

surgery. The patient had had rheumatic fever some twenty years previously and had suffered bouts of congestive failure for the past two years despite digitalization and low-salt diet. The mitral first sound was loud and preceded by a long rumbling diastolic murmur. Auricular fibrillation was present. Despite intensive treatment his lungs were never completely free of râles. He developed psychotic episodes for a few days. On June 16, 1954, a commissurotomy was performed and the auricular appendage was found to contain a large dense clot. An 80 Gm. piece was dissected from the posterior wall. At this time his condition became precarious and the mitral valve was rapidly fractured. It was found to be heavily calcified. No regurgitation was noted before or after the fracture. Almost at once ventricular fibrillation developed, followed by asystole, and despite defibrillation and various medications, the patient succumbed.

Post-mortem examination (A-54-66) showed the endocardium of the left atrium to be markedly roughened. The mitral valve was markedly calcified with rolled edges (Fig. 3). The orifice was narrowed to a slit measuring 2.8 cm. A medial fracture line measuring 1.0 cm. and a posterolateral fracture line measuring 0.5 cm. were seen, however, in the same approximation as previous to the fracture.

Comment.—Apparently the trauma of removing such a large ante-mortem clot was more than the conduction system of a diseased heart under anesthesia could handle. Glover advocates the removal of only loose granular thrombotic material in the appendage, and not all of the thrombus.⁹ If this patient had lived one might wonder whether the margins would have soon adhered and returned to their former state.

CASE 4.—(MMH-382836) This 51-year-old, white, married street car guard was admitted to the surgical service on Oct. 19, 1955, for mitral commissurotomy with no known history of rheumatic fever. For the past three years he had suffered progressive symptoms of congestive failure necessitating digitalization. His physician advised mitral surgery which the patient had refused six months previously. On physical examination a Grade 3 diastolic murmur was heard at the apex with a palpable thrill. ECG showed right ventricular strain. Chest x-ray showed cardiomegaly with left atrial enlargement and congested lung fields with left pleural effusion. On Oct. 24, 1955, the patient underwent a mitral valvulotomy. Following fracture of a heavily calcified anterior commissure the blood pressure became unobtainable and further efforts were desisted since an adequate opening was obtained. Heart action seemed strong and regular even though blood pressure was still unobtainable, and there were no spontaneous respirations. Patient was started on Levophed and placed in a respirator. Four hours later spontaneous respirations and blood pressure had returned. The next morning the pupils were unequal and fixed, and that afternoon the patient expired.

At post-mortem examination (A-55-148) small, friable, calcific fragments were seen on a markedly calcified mitral valve. A small, hard, occluding clot containing calcium deposits was seen in the right posterior vertebral artery.

Comment.—It is interesting that a fragment of the valve embolized to the posterior vertebral artery since the common carotid arteries were not occluded at surgery.

CASE 5.—(MMH-379158) This 49-year-old white housewife was admitted to Evans Memorial Hospital on March 5, 1955, with chief complaints of increasing exertional dyspnea and "chest discomfort" for the past six weeks, despite digitalization by her private physician. X-ray showed an enlarged right ventricle, left auricle, and mitral calcification. No history of rheumatic fever was elicited. Auricular fibrillation was present with a blowing diastolic murmur at the apex. No edema was present. On March 15, 1955, a mitral commissurotomy was performed. Immediately prior to entering the left atrium for finger fracture, the heart beat showed marked irregularity and the commissurotomy was rapidly completed. Thereafter, the heart showed ventricular flutter, asystoles, continued auricular fibrillation, and ventricular fibrillation at various

times. After prolonged manual massage and various medications, heart action improved and sutures were closed. That evening the patient suddenly vomited with aspiration and, despite tracheotomy, oxygen, and medication, the patient succumbed.

On post-mortem examination (A-55-35) the papillary muscles of the left ventricle were bruised and purple with one ruptured chorda tendinea.

Comment.—This case may not have warranted a commissurotomy, assuming the stenosis was slight enough that the finger bruised papillary muscles, or else in haste the procedure was done too vigorously and in this way caused damage.



Fig. 4.—Case 6. The opened aortic valve demonstrates rolled shortened cusps accompanied by regurgitation. The accessory valve on the left ventricular wall is indicated by the arrow.

CASE 6.—(MMH-382267) This was the third MMH admission of this 22-year-old white, single women complaining of angina pectoris of four months' duration. She had suffered rheumatic fever at age 4 years. At age 8 years she was treated at the Haynes Memorial Hospital for meningitis and subacute bacterial endocarditis and, following discharge, was carried on prophylactic penicillin. At age 17 years she was treated for active rheumatic fever with carditis. Seven months prior to her final admission she was digitalized because of exertional dyspnea. Anginal pains later developed requiring nitroglycerine for relief. A Grade 3 systolic murmur was heard at the base of the heart together with a Grade 3 diastolic murmur at the left sternal border. Also a Grade 2 systolic murmur was heard at the apex. A systolic thrill was felt over the sides of the neck and base of the heart. Râles were heard at the base of both lungs. Blood pressure was 110/60 mm. Hg. ECG showed left bundle branch block. X-ray showed an enlarged heart with a prominent left ventricle. Cardiac catheterization showed some degree of aortic insufficiency. Because her diastolic pressure was not low enough to explain her angina, her main disease was believed to be aortic stenosis rather than insufficiency. On Sept. 22, 1955, pressure readings were

taken in the left ventricle and the aorta with a determinate of 30. While clamps were being fitted to the aorta to explore the valve, the patient developed cardiac arrest and ventricular fibrillation and expired.

Post-mortem examination (A-55-127) showed no aortic stenosis but, rather, insufficiency with the cusps appearing like a thick rolled cord (Fig. 4). A pseudovalve measuring 3 cm. in diameter was seen on the endocardium below the aortic cusps. Microscopically the smaller coronary arteries were quite thickened; the larger arteries were of normal size.

Comment.—The true cause of the angina was undoubtedly due to thickened, small coronary arteries.

CASE 7.—(MMH-353779) This 32-year-old, white, single, male office worker was admitted to the surgical service of MMH on Sept. 17, 1951, for a mitral valvulotomy. Patient suffered rheumatic fever at age 8 years and for the past ten years had suffered progressive symptoms of congestive failure which interfered with his work and necessitated digitalization and low-salt diet. Cardiac catheterization studies done in the spring of 1951 were favorable for surgical intervention. However, one month later he was treated for a bout of rheumatic activity and developed auricular fibrillation, requiring an increase in digitalis dosage. On physical examination auricular fibrillation was present, the chest was clear, and Grade 2 aortic systolic and diastolic murmurs were also heard. ECG showed left atrial dilatation with right ventricular strain and digitalis effect. On Sept. 18, 1951, a commissurotomy was performed. The mitral orifice was found to be extremely small and no regurgitation was noted. An adequate opening was accomplished. Blood pressure dropped at this point and remained low despite neosynephrine. However, one hour postoperatively blood pressure returned to its previous levels. Approximately two hours later an increase in the amount of blood in the underwater seal bottle was noted together with a fair amount of bleeding from under the chest dressing. Another two hours later blood pressure began to fall and the chest was reopened. A fair-sized bleeder was clamped in the muscle layer before incising the perichondral sutures. Several hundred cubic centimeters of bloody fluid were seen in the left pleural cavity. As the pericardium was being inspected, ventricular fibrillation developed, blood pressure fell, and despite various procedures the patient soon succumbed.

Post-mortem examination (A-51-111) showed a small laceration measuring 0.4 cm. in length near the base of the left auricle, through which a probe could be passed into the left ventricle and from which blood escaped on pressure.

Comment.—The superimposed trauma of re-entering the chest and pericardial cavity in a diseased postoperative heart may be blamed for this person's death.

DISCUSSION

These cases represent a variety of causes of death. In the early days of commissurotomy the most common cause of death was due to problems with the surgical technique. Today, with improvement of the technique, which of course is still being perfected, new problems are becoming evident. These are missed preoperative diagnosis, inadequate preoperative studies, inaccurate patient evaluation, accompanying congenital heart defects, anesthesia, and the past experience of the anesthetist with cardiac patients. Therefore it will be through the combined efforts and expert advice of internists, surgeons, anesthetists, and radiologists that patients will successfully undergo cardiac surgery.

SUMMARY

Seven cases of unusual cardiac deaths in patients undergoing mitral or aortic valve operations are presented, including production of ball-valve thrombus,

undiagnosed Lutembacher's syndrome, traumatic removal of large atrial thrombus, embolization to the right posterior vertebral artery, and a surgically ruptured chorda tendinea of a relatively patulous mitral valve.

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A THEORETICAL ELUCIDATION OF THE NOTION "VENTRICULAR GRADIENT"

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IT MAY be supposed as generally known that the spatial ventricular gradient is the time integral of the heart vector \vec{H} :

$$\vec{G} = \int \vec{H} dt \quad (1)$$

It is the vectorial sum of the infinitesimal small products of the heart vector \vec{H} and the infinitesimal small time interval dt . It can be extended over the period of depolarization (QRS), over the period of repolarization (T) or over the total heart period:

$$\vec{G}_{QRS-T} = \vec{G}_{QRS} + \vec{G}_T \quad (2)$$

The sum has to be taken as a vectorial one.

The vectorial ventricular gradient owes its significance to the allegation that its value depends only on the state of the heart muscle and is independent of the origin of the excitation. So it should be a means to discriminate between a failure of the heart muscle and of the Purkinje system. The clinical significance of the gradient must remain undiscussed here.

In view of equation (1) the name "gradient" is paradoxical. While this word denotes in physics a differential quotient with respect to position or a coordinate it appears here as indicating an integral with respect to time. It is the purpose of this paper to show that, in a schematic case, \vec{G} defined according to (1) has, indeed, a relation to a gradient in the physical meaning.

We will consider first the schematic case of a narrow homogeneous muscle strip as depicted in Fig. 1. An analogous case was treated some years ago by

Wilson² and by Cabrera.¹ The present one, however, is somewhat less specialized. It is supposed that the boundary between depolarized and repolarized muscle tissue is a plane perpendicular to the strip. So the "heart vector" has the direction of the strip and is supposed to have a constant magnitude, the same for the depolarization and the repolarization wave.

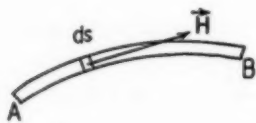


Fig. 1.—Excitation of a muscle strip AB , beginning at A . ds = element of muscle strip. \vec{H} = heart vector.

If the depolarization (*QRS*) is started at *A* (Fig. 1), the gradient of depolarization can be calculated according to equation (1):

$$\vec{G}_{QRS} = \int \vec{H} dt \quad (2a)$$

We assume the velocity of propagation of the depolarization to be constant (*c*). Then the length of an infinitesimally small element *ds* of the strip equals the product of velocity *c* and time *dt*:

$$ds = c dt, \text{ or } dt = ds/c. \quad (3)$$

This substituted in (2) gives:

$$\vec{G}_{QRS} = \int_A^B \frac{\vec{H} ds}{c} = \frac{1}{c} \int_A^B \vec{H} ds.$$

As \vec{H} and \vec{ds} (considered as a vector) have the same direction, we can put the arrow over \vec{ds} as well as over \vec{H} :

$$\vec{G}_{QRS} = \frac{1}{c} \int_A^B \vec{H} ds.$$

H, the magnitude of the "heart vector" is supposed to be constant, so:

$$\vec{G}_{QRS} = \frac{H}{c} \int_A^B \vec{ds}. \quad (4)$$

The vectorial sum of all elements \vec{ds} is the vector \vec{AB} , independent of the shape of the arbitrarily curved muscle strip, and therefore:

$$\vec{G}_{QRS} = \frac{H}{c} \int_A^B \vec{ds} = \frac{H}{c} \vec{AB} \quad (5)$$



Fig. 2.—Excitation of a muscle strip, beginning at *C* and proceeding to *A* and *B*.

If the starting point of the excitation is not at the end of the strip but in arbitrary point *C* (Fig. 2) we can consider both parts *CA* and *CB* separately. According to equation (4) we have then:

$$\vec{G}_{QRS} = \frac{H}{c} \int_C^A \vec{ds} + \frac{H}{c} \int_C^B \vec{ds} = \frac{H}{c} (\vec{CA} + \vec{CB}).$$

It can be easily seen that this vector sum generally depends on the position of the starting point *C* on the muscle strip *AB*.

After the depolarization (= excitation) there follows repolarization. If the time τ taken by the muscle tissue to repolarize is constant all over the strip, it is easily seen that the repolarization process follows the depolarization with the same velocity *c*. The only difference is that now the direction of the vector \vec{H} is reversed. So:

$$(\int \vec{H} dt)_{\text{rep.}} = - (\int \vec{H} dt)_{\text{dep.}} \quad \text{or}$$

$$\vec{G}_T = - \vec{G}_{QRS}, \quad \text{and}$$

$$\vec{G}_{QRS-T} = 0$$

We have, therefore, to accept some heterogeneity as to the time of repolarization τ , in order to be able to explain a finite value of \vec{G}_{QRS-T} . We will, therefore, suppose henceforth that the time of repolarization τ is a function of the position on the muscle strip.

In order to realize the consequence of this supposition we return to the simple case of Fig. 1, where the depolarization starts at the beginning A of the muscle strip. When τ does not depend greatly on the position, i.e., on s , the distance of a point from A measured along the strip, the repolarization follows the same course from A to B . But the velocity is not c ; it can be calculated in the following way.

If s is again the length of the muscle strip from A to an arbitrary point P on it, the depolarization, starting at A , takes a time s/c to reach P . If $\tau(s)$ is the time taken for the repolarization, depending on the position of P and so on the length s , the repolarization takes place at the time $s/c + \tau(s)$, after the starting of the depolarization at A . So:

$$t_{\text{rep.}} = s/c + \tau(s).$$

By differentiating this equation with respect to s , we obtain:

$$\frac{(dt)_{\text{rep.}}}{ds} = \frac{1}{c} + \tau'(s),$$

when $\tau'(s) = \frac{d\tau(s)}{ds}$ is the derivative of the function $\tau(s)$.

Now $ds/(dt)_{\text{rep.}}$ is the velocity $c_{\text{rep.}}$ of the repolarization wave T , so:

$$\frac{1}{c_{\text{rep.}}} = \frac{1}{c} + \tau'(s) \quad (6)$$

The contribution of the T wave to the spatial ventricular gradient is expressed by the general equation (1), but since \vec{H} and \vec{ds} have now an opposite direction, we get:

$$\vec{G}_T = - \int_A^B \vec{H} dt = - \int_A^B \vec{H} \frac{ds}{c_{\text{rep.}}}$$

$1/c_{\text{rep.}}$ can be replaced by its value according to (6), and $\vec{H} ds$ can be written as $H \vec{ds}$ just as in the QRS case. Then we obtain:

$$\vec{G}_T = -H \int_A^B \vec{ds} \left\{ \frac{1}{c} + \tau'(s) \right\} = -H \int_A^B \frac{\vec{ds}}{c} - H \int_A^B \tau'(s) \vec{ds}.$$

The first integral can be evaluated as in the preceding case:

$$-H \int_A^B \frac{\vec{ds}}{c} = -\frac{H}{c} \int_A^B \vec{ds} = -\frac{H}{c} \vec{AB}.$$

According to (2) the total ventricular gradient is:

$$\vec{G}_{QRS-T} = \vec{G}_{QRS} + \vec{G}_T = \frac{H}{c} \vec{AB} - \frac{H}{c} \vec{AB} - H \int_A^B \tau'(s) \vec{ds} = -H \int_A^B \tau'(s) \vec{ds}. \quad (7)$$

From this equation we can only derive a distinct result, if we suppose that $\tau'(s)$ is constant along the muscle strip AB . Then (7) reduces to:

$$\vec{G}_{QRS-T} = -H\tau'(s) \int_A^B \vec{ds} = -H\tau'(s) \vec{AB}. \quad (8)$$

In order to understand the next step, it should be borne in mind that $\tau'(s)$ is positive if the time τ increases from A to B . This next step is that we return to the situation of Fig. 2, where the excitation starts at an arbitrary point C of the muscle strip. From C the excitation proceeds along the muscle strip to A and to B . Both processes give their contribution to \vec{G} according to (8). For the propagation from C to B we can apply (8) directly and have:

$$(\vec{G}_{QRS-T})_{CB} = -H\tau'(s) \vec{CB} \quad (9a)$$

But for the propagation from C to A the direction of the propagation has a sign opposite the direction in which $\tau'(s)$ is taken positive. We must, therefore, give $\tau'(s)$ in this integral a negative sign, but according to our assumption the same value as in the preceding case, so:

$$(\vec{G}_{QRS-T})_{CA} = +H\tau'(s) \vec{CA} \quad (9b)$$

The total gradient is the sum of the contributions (9a) and (9b):

$$\vec{G}_{QRS-T} = H\tau'(s) (\vec{CA} - \vec{CB}) = H\tau'(s) (\vec{CA} + \vec{BC}) = H\tau'(s) \vec{BA}. \quad (10)$$

From (10) the important conclusion may be drawn that the ventricular gradient, which takes all our assumptions for granted, is independent of the position of the point C , the starting point of the excitation. It is this property that gives the gradient its importance.

Two remarks may be made with respect to equation (10): (a) The gradient is proportional to the differential quotient $\tau'(s)$, which is a real gradient, i.e., a differential quotient of a property τ of the muscle with respect to a "coordinate" s . For a homogeneous muscle strip the gradient is zero; (b) We may suppose that the retardation time τ of the repolarization is greater the more the muscle is injured or strained. If the strain is greatest at B then the time τ is greatest there and $\tau'(s)$ is positive. Then \vec{G} has, according to (10), the same direction as \vec{BA} , so the gradient is directed from the more injured or strained part B to the less injured or strained part A .

The muscle strip, dealt with above, may be curved and may even be curved in space. It need not be flat. So we have solved a spatial problem;

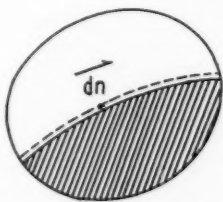


Fig. 3.—Heart muscle partly depolarized (shaded). The excitation proceeds along a normal of the boundary surface between polarized and depolarized. \vec{dn} = infinitesimally small element of normal. This is a vector whose direction gives the direction of propagation of the excitation.

but on the other hand it is a linear object, although curvilinear. It is possible, however, to solve the problem with some restrictions for a real spatial case, i.e., for a muscle mass extending in three dimensions and having an arbitrary shape. But in this case we need more mathematics than in the preceding one. In the schematic (Fig. 3) part of the muscle mass (shaded) is excited. As the depolarization is depicted, the shaded part is increasing.

As in the former case, we suppose that the boundary between excited and nonexcited is sharp (Durrer and Van der Tweel²). This boundary surface may be described by the equation:

$$F(x, y, z, t) = 0.$$

x , y , and z are orthogonal coordinates, and t is the time. The occurrence of t in this equation means that the boundary surface depends on time, i.e., that it proceeds.

In order to make the calculation as simple as possible we think t resolved from the last equation:

$$f(x, y, z) = t \quad (11)$$

The way in which f is derived from F is of no importance for the following deductions. By equation (11) is expressed that, at each moment, for any value of t , the shape of the boundary surface is determined and dependent upon t . At a time $t' = t + dt$, somewhat later than t , the boundary surface has proceeded and is depicted by the dotted line, which represents a cross section of this surface and the plane of the drawing. By means of elementary analytic geometry it can be shown that the small distance dn of the two surfaces at the point $P(x, y, z)$ is:

$$dn = \frac{dt}{\left\{ \left(\frac{\partial f}{\partial x} \right)^2 + \left(\frac{\partial f}{\partial y} \right)^2 + \left(\frac{\partial f}{\partial z} \right)^2 \right\}^{\frac{1}{2}}} \quad (12)$$

$\frac{\partial f}{\partial x}$, $\frac{\partial f}{\partial y}$, $\frac{\partial f}{\partial z}$ are the partial differential quotients of the function f , with respect to x , y , z . The equation (12) can be used to express dt in a linear quantity dn in a way analogous to that in the case of the muscle strip.

We first calculate the depolarization part of the gradient:

$$\vec{G}_{QRS} = \int_{QRS} \vec{H} dt \quad (2a)$$

According to (12) dt may be substituted:

$$dt = dn \left\{ \left(\frac{\partial f}{\partial x} \right)^2 + \left(\frac{\partial f}{\partial y} \right)^2 + \left(\frac{\partial f}{\partial z} \right)^2 \right\}^{\frac{1}{2}} \quad (12a)$$

The heart vector \vec{H} at the moment t is a surface integral, extending over the boundary surface $t = f(x, y, z)$. If dS is an infinitesimal element of this surface, the contribution of dS to the heart vector \vec{H} is $\vec{h} dS$. In this product \vec{h} is a vector, directed normally to the surface $t(x, y, z)$ and from excited to unexcited. It is well known that the amount of \vec{h} , denoted by h , in various cases is not much different and of the order of magnitude of 100 mv. It is the potential jump at the boundary layer. We will suppose it to be constant, i.e., independent of place and time during the propagation of the boundary surface.

The total heart vector is the surface of $\vec{h} dS$, extended over the area of the surface $t = f(x, y, z)$:

$$\vec{H} = \int_S \vec{h} dS \quad (13)$$

Substitution of (12a) and (13) in (2a) gives:

$$\vec{G}_{QRS} = \int \int_S \vec{h} \left\{ \left(\frac{\partial f}{\partial x} \right)^2 + \left(\frac{\partial f}{\partial y} \right)^2 + \left(\frac{\partial f}{\partial z} \right)^2 \right\}^{\frac{1}{2}} dn dS \quad (14)$$

The first integral sign denoted originally an integration with respect to time, but by the conversion (12a) it is now a spatial integration, and both integral signs can be replaced by an integration over the volume of the muscle. This is in accordance with the fact that $dn dS$ is volume element, a small cylinder with dS as base and dn as height:

$$dn dS = dv.$$

So \vec{G}_{QRS} is a volume integral:

$$\vec{G}_{QRS} = \int_{vol} \vec{h} \left\{ \left(\frac{\partial f}{\partial x} \right)^2 + \left(\frac{\partial f}{\partial y} \right)^2 + \left(\frac{\partial f}{\partial z} \right)^2 \right\}^{\frac{1}{2}} dv \quad (14a)$$

In order to transform this integral so that it is suited for calculation of \vec{G}_T , we can introduce the *gradient* of f . This is a vector, the components of which are the differential quotients $\frac{\partial f}{\partial x}, \frac{\partial f}{\partial y}, \frac{\partial f}{\partial z}$. It is denoted by $\vec{\nabla} f(x, y, z)$ or more simply by $\vec{\nabla} f$. Its value is computed from the components in the ordinary way as square root of the sum of the squares of the components:

$$|\vec{\nabla} f| = \left\{ \left(\frac{\partial f}{\partial x} \right)^2 + \left(\frac{\partial f}{\partial y} \right)^2 + \left(\frac{\partial f}{\partial z} \right)^2 \right\}^{\frac{1}{2}}$$

Before substituting this in (14a), we may remark that the direction of $\vec{\nabla} f$ is the same as that of the normal (\vec{dn} , Fig. 3) on the surface $t = f(x, y, z)$. This follows immediately from the well-known expression of differential analytic geometry. Since \vec{h} has the direction of the normal too, we can transform the integrant of (14a) in this way:

$$\vec{h} \left\{ \left(\frac{\partial f}{\partial x} \right)^2 + \left(\frac{\partial f}{\partial y} \right)^2 + \left(\frac{\partial f}{\partial z} \right)^2 \right\}^{\frac{1}{2}} = h \vec{\nabla} f$$

and since h is a constant, we get:

$$\vec{G}_{QRS} = h \int_{vol} \vec{\nabla} f dv. \quad (15)$$

This simple formula allows us to compute the rest of the gradient, \vec{G}_T . To this end we suppose again that repolarization follows depolarization after a time τ . This time is in the present case a function of the place in the muscle so it is a function $\tau(x, y, z)$ of the coordinates. With assumptions analogous to those made in the first part, the propagation of the boundary surface, on the analogy of equation (11), can now be expressed by:

$$t = f(x, y, z) + \tau(x, y, z). \quad (16)$$

Since in repolarization (T), accepting our simplifying assumptions as in the first case, \vec{h} has just the opposite direction as in depolarization, substitution of (16), i.e., $f + \tau$ for f in (15), gives:

$$\vec{G}_T = -h \int_{\text{vol}} (\vec{\nabla} f + \vec{\nabla} \tau) dv. \quad (17)$$

Addition of (15) and (17) gives the total ventricular gradient:

$$\vec{G}_{QRS-T} = -h \int_{\text{vol}} \vec{\nabla} \tau dv. \quad (18)$$

If $\vec{\nabla} \tau$ is constant over the whole muscle, we can write it before the integral sign and, keeping in mind that $\int_{\text{vol}} dv = V$ is the total muscle volume, the gradient amounts to:

$$\vec{G}_{QRS-T} = -h V \vec{\nabla} \tau. \quad (18a)$$

From the formulae (18) and (18a) it appears that the starting point of the depolarization has no influence on the gradient. This influence is present in both parts \vec{G}_{QRS} and \vec{G}_T as it is represented by the function $f(x, y, z)$. But the total gradient depends only on the lag time τ , in the state of the myocardium. It is interesting to remark that in the final result it is the *gradient* of this time that determines \vec{G} . The name gradient appears to be well chosen; the word has the same meaning as in physics.

The direction of \vec{G}_{QRS-T} follows from (18a). It points from parts of the muscle with greater τ to such with smaller τ . So it is directed from the more injured or strained part to the less injured or strained part, just as in the first case, that of the narrow muscle strip.

SUMMARY

In simple cases it can be shown, theoretically, that the ventricular gradient is independent of the point of excitation. It can be expressed in the gradient of the time interval between depolarization and repolarization.

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ON CONSISTENCY IN CONVENTION OF "VIEW" IN VECTORCARDIOGRAPHY

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INTRODUCTION

IN A PREVIOUS paper¹¹ good reasons were put forward for adopting positive convention of sign in electrocardiography and vectorcardiography. It was demonstrated that, during the wave of accession (QRS complex), an applied electrode is positive; that, in fact, movement (of the 'wave of negativity') from the zero-point toward the (unipolar) applied electrode must be shown as positive; and, conversely, movement away from the applied electrode is negative. The former is shown, in the scalar electrocardiogram, as a deflection 'above the line' of zero-potential, and the latter as a 'below the line' deflection. It was also shown that there is no essential difference between unipolar and bipolar leads; and this is now generally accepted. The present communication extends these arguments so as to suggest logical 'points of view' for the representation of vectorcardiograms in the frontal, sagittal, and horizontal (coronal) planes.

PROPOSITION

With a normally positioned heart the wave of accession in the ventricles, represented by the spatial QRS vector, moves (from the zero-point) downward, to the left, and usually forward. This spatial vector is projected on to the three planes in the manner of Fig. 1. That is to say: (a) In the frontal plane the vector goes downward and to the left. Its sagittal plane component is going *toward* the observer—unless indeed the frontal plane is regarded as "from behind," which is obviously not desirable. For the same reason it is immaterial whether, in fact, the apex of the heart points anteriorly or posteriorly, for the frontal plane would be regarded "as from the front" in any system of viewing; (b) In the sagittal plane the vector will also go *toward* the observer if this plane is regarded as from the left; (c) In the horizontal (coronal, or transverse) plane it will again be moving toward the observer if the viewpoint is as from below.

It is suggested that, just as for an applied electrode, movement toward the observer should be represented as a positive deflection in each of the three planes. If that is accepted, then the 'point of view' for each plane must be as stated above.

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Alternatively, the three spatial planes can be shown as intersecting at the zero-point, as illustrated in Fig. 2.

It will be noted that the crux of this argument is that the "correct" viewpoint for the sagittal plane component of the spatial QRS vector is from the left, which clearly indicates movement toward the observer.

A. *A Special Consideration Affecting the Representation of the Horizontal (Coronal, or Transverse) Plane.*—Even though it may be agreed that the horizontal plane shall be viewed as from below, it is still possible to show this plane in two ways (Fig. 3). The vertebral column may be shown either as 'below,' or as 'on top,' with standard chest leads positioned as indicated in the figure. Such possible ambiguity cannot arise for the frontal and sagittal planes, for no one would suggest that the subject is to be depicted as standing on his head.

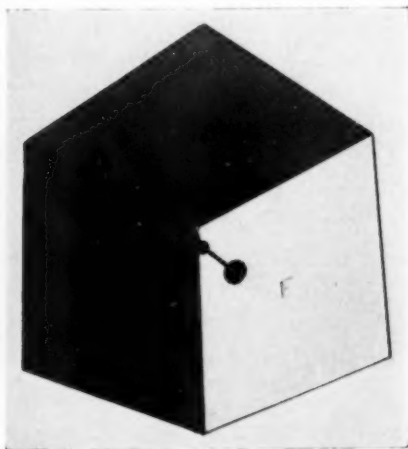


Fig. 1.

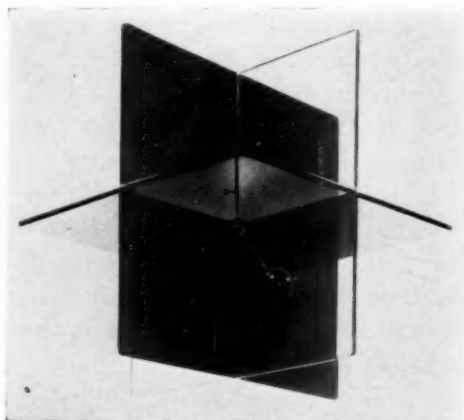


Fig. 2.

Fig. 1.—Left oblique view, and somewhat from below. With a normally positioned heart, voltages (i.e., a negative "wave front") moving toward the observer are always positive, and should always be recorded as upright (above the isoelectric line) in the scalar, derived, electrocardiogram—as is agreed current practice.

Fig. 2.—The same as Fig. 1, but with the three spatial planes transposed to intersect at the zero-point.

The preferred representation is the former (Fig. 3,A), with the vertebral column shown at the bottom of the picture, for reasons which become apparent in the next section of this paper.

CRITICAL REVIEW

Although Shillingford and Brigden¹² appear to have quite clear ideas regarding polarity, yet, by recording a scalar lead (curve A of their Fig. 6) "upside down," they have watered the seeds of some confusion, originally sown by Duchosal,³ and shown in full flower in the writings of Fischmann.^{4,5} It would have been better if they had shown curve A, which represents craniocaudal voltages in the frontal and sagittal planes, "normally" upright, and reorientated it, for vectorcardiographic inscription, in a similar way to their representation of curve B.

Although hardly germane to the present argument, it is noted that all Shillingford and Brigden's vectorcardiograms appear unduly "elongated" (but see below). This is because they have adopted Duchosal's system of lead placement, based on his "parallepipède" (see Fig. 34 of Duchosal and Sulzer's³ monograph); but inspection of his Fig. 29³ clearly shows how much distortion of the frontal plane vector loop is caused by this practice. It is unfortunate that this lead placement was chosen, in view of the thorough preliminary experimental work that was carried out (see Duchosal and Sulzer,³ Chapter 5); their level 'E' would, in my view, have been more satisfactory.

This point is clearly recognized by Grishman, Borun, and Jaffe,⁹ and their polarities are as recommended here, even though their "points of view" for the sagittal and coronal planes are different (sagittal from the right; horizontal from above). Their vectorcardiograms have none of this "elongated" appearance.

In subsequent papers^{13,14} Shillingford and Brigden realized this distortion, and adopted the same electrode positions as Grishman, Borun, and Jaffe.

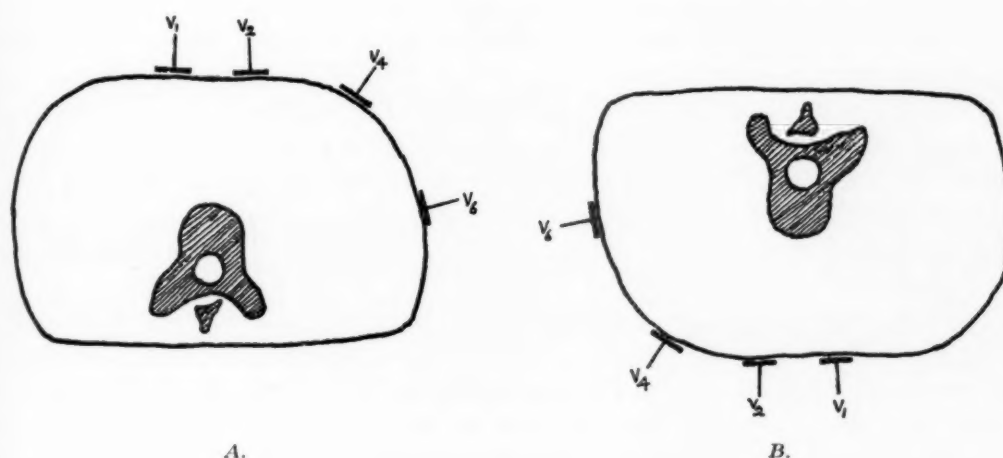


Fig. 3.—Two ways of depicting horizontal (coronal) plane vectorcardiograms when viewed from below. A is regarded as preferable, for reasons discussed in the text.

Fischmann⁵ has become confused, I think, because he also records craniocaudal voltages as "upside down" in the scalar electrocardiogram. Moreover, in speaking of the "caudo-cranial lead," and in showing craniocaudal voltages as going headward (Fig. 3), he reverses Einthoven's polarities for bipolar leads—even though the craniocaudal vector is correctly indicated in Fig. 1.

Further evidence of confusion is shown by Fig. 2, where the small addition to Wenckebach and Winterberg's original figure shows vectors going anteriorly (added figure at + 135 degrees) as positive, whereas the same forwardly proceeding vectors are shown as negative in another figure (that at + 45 degrees).

Fischmann's later paper⁴ is also marred by this same feature; headward-going voltages are shown as positive (see his Fig. 1); and here again he speaks of the "caudo-cranial lead." This again reverses Einthoven's conventions, which regard voltages proceeding toward the left arm and voltages proceeding toward the left leg (for the frontal plane) as positive, in each case. Moreover,

Einthoven always shows positively proceeding voltages as upright in his scalar curves, as is universal practice in electrocardiography; and this should certainly not now be abandoned. Fischmann⁵ could equally well have shown his Figs. 1 and 4 with y voltages recorded upright, and Ef drawn (Fig. 1) as from the tip of the y vector.

It would appear that this confusion arises because the essential relations between the bipolar and unipolar leads of the scalar electrocardiogram are not clearly expressed. Reference may be made to Section 3 of a previous paper of mine.¹¹ Movement away from the zero-point and toward the observer (as illustrated by Fig. 1¹¹) will be shown as a positive deflection; movement from the zero-point and away from the observer will be shown as a negative deflection. Furthermore, *any* movement *toward* the observer will be shown as positive (with unipolar or bipolar leads); and any movement away from the observer will be shown as negative—quite irrespective of the zero-point.

Grishman and his associates,⁹ using their "cube" system of electrode placement (and bipolar leads), regard the sagittal plane as from the right, and the horizontal plane as from above.

Goldberger⁶ also views the sagittal plane from the right and the horizontal plane from above. But for the horizontal plane this makes his viewpoint opposite to his viewpoint for describing rotations of the heart about its long axis, as he himself is careful to point out (Ref. 6, page 477). Would it not have been less confusing, and more consistent, if he had regarded the horizontal plane as from below?

Burch and associates² make little use of the horizontal plane; but when they do use it, it is viewed 'from above.' The sagittal plane they recommend to be viewed as from the right; nevertheless, in the later parts of their monograph this plane is usually regarded as from the left.

Shillingford and Brigden¹²⁻¹⁴ regard the horizontal plane from below, but the sagittal plane from the right.

Grant and Estes⁸ adopt the "views" advocated here.

It is apparent that the present recommendations are, as regards the horizontal (transverse) plane, contrary to those of the 1954 Committee of the American Heart Association.¹⁶ But, in this particular, a careful study of their report does not suggest that their recommended choice of view (sagittal from the left; horizontal from above) is anything other than arbitrary. This Committee states (Ref. 16, page 571): "A good deal of misunderstanding exists with regard to the polarity of the leads to be used in any vectorcardiographic reference system. This arises largely from confusion of the direction of motion of the cathode ray when the standardizing voltage is applied with the direction of this motion which results when a voltage obtained from the body is applied."

"The conventions to be followed are relatively simple and logical if the source of the cardiac electromotive force is regarded as being a single point. Initially the cardiac vector can only have a direction in three-dimensional space away from this point of zero reference. Under these circumstances the point in question must always be initially electronegative with respect to any other point in the body."

This statement appears to be self-evident. But it ignores one vital point—the convention of Einthoven. In this, of course, headward going voltages are never positive; and Lead II is shown "illogically" reversed. Left leg voltages are always positive, both for Lead II and for Lead III.

A further excerpt from the Committee's report is relevant. They state (Ref. 16, page 572), with regard to unipolar leads: "If the body is viewed from above, and a point on the back is regarded as yielding the z component, the exploring electrode is attached to the posterior plate; but if a point on the front of the chest is used for this component, the exploring electrode is attached to the corresponding anterior plate." This is also illogical, and will lead to discrepancies between unipolar and bipolar leads. In the horizontal (and the sagittal) plane anteriorly going vectors should always be positive, and posteriorly proceeding vectors always negative.

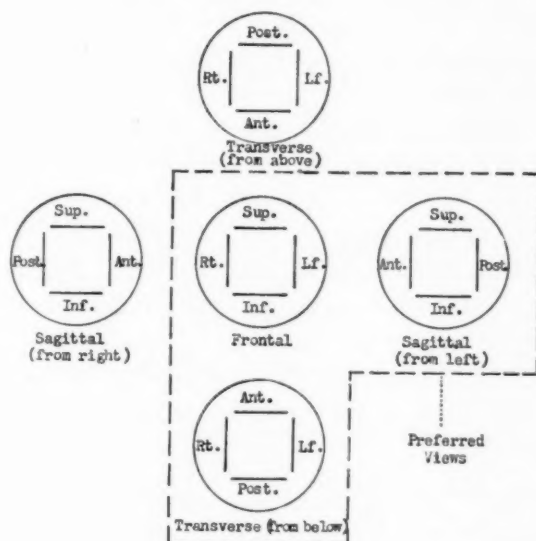


Fig. 4.—Recommended "views" for each of the three planar projections of spatial vectorcardiograms. Figure modified from that illustrating the 1954 American Heart Association Committee's recommendations (see Ref. 16).

It seems certain that Einthoven was mainly concerned that the principal deflections should appear upright in his finished normal tracings. This is also discussed in Section 3 of a former publication,¹¹ as well as the relations between unipolar and bipolar leads. There is, in fact, no essential difference between unipolar and bipolar leads. Essentially, bipolar leads take into account the "negative" component, as well as the "positive" component of the lead. (See also Grant and Estes,⁸ page 20).

It is hoped that this, or an equivalent, Committee may be induced to reconsider their decision. Modifying the Committee's Fig. 1,¹⁶ Fig. 4 of the present article makes clear which are here put forward as the proposed "points of view" for the three planes.

It will be noted, further, that this Committee has made no reference to alternative representations for the horizontal (transverse) plane, whether regarded from below or from above, though their preferred representation is

implied from a consideration of their Fig. 1 (see Section A, under "Proposition," and Fig. 3 of this article). In this particular it is considered that their choice is correct, because the correct representation is suggested by the consistent showing of the patient's left side as being on the right of the diagram, and determined essentially by the obvious representation of the frontal plane (Fig. 4; and Ref. 16, Fig. 1).

Another way of deciding this point is to regard the patient, lying supine, as from the footward end of the examining couch¹⁷; and it will be noted that such a view also determines the recommended view of the horizontal plane being as from below. (Nevertheless this gives no guidance regarding the viewpoint for the sagittal plane).

Recently Helm¹⁰ has published a paper which approaches the problem from the trigonometric point of view. His conclusions are the same as mine, and he points out that to regard the sagittal plane from the left while regarding the transverse (horizontal) plane from above (or to regard the sagittal plane from the right and the transverse plane from below) causes inconsistency of sign of angle. He, too, puts forward a plea that the American Committee¹⁶ should reconsider their recommendation. I would select Helm's second 'consistent' recommendation as preferable; in his Fig. 5B the sagittal plane is regarded as from the left, and the transverse (horizontal) plane as from below.

A. *Plane Vectorcardiography and Lead Electrode Placement.*—No agreement has yet been reached as to what is the ideal lead arrangement, and I agree with Bayley¹ that "suggestions for the standardization of vectorcardiographic leads at this time are premature." Nevertheless a superficial examination of the problem is relevant to the present argument.

Broadly speaking, present vectorcardiographic lead arrangements fall into two main categories:

1. Rectilinear arrangements—e.g., those of Grishman and associates⁹ and Duchosal.³
2. Arrangements based essentially on Einthoven's triangle (for the frontal plane, or frontal plane parallel)—e.g., the equilateral tetrahedron of Wilson and associates,¹⁵ where there is only one electrode defining voltages in depth.

In the former case one can quite properly speak of the sagittal and horizontal plane projections of the spatial vector. But in the latter there can be no true sagittal or horizontal planes, since both are tilted out of their rectilinear axes.

Nevertheless, whatever lead placement or determination of zero-potential may be eventually agreed, it will, I think, be profitable to standardize "view-points" on a broad basis, so that vectorcardiograms can appear approximately similar in each of the three planes, whatever the system of leading.

It may be that no universally accepted standards will be found, and it does not, in any case, appear likely that vectorcardiography will ever become greatly adopted for everyday clinical use, offering as it does so few, if any, advantages over ordinary scalar lead electrocardiography. And, if two simultaneous scalar leads are recorded, any phase difference between them, shown

vectorcardiographically as the looping of the vector, is apparent; and all the additional information given by a vectorcardiogram is certainly evident. This is particularly well demonstrated by Fischmann.^{4,5}

But even if vectorcardiography is unlikely to have much practical use, it has considerable advantages as a method of mental synthesis of scalar lead electrocardiograms; this is especially evident in the writings of Grant.⁷⁻⁸

SUMMARY

1. On the simple basis that movement of the cardiac impulse (represented by a vector) toward the observer is positive in sign, it is argued that in vectorcardiography: (a) the frontal plane should be regarded as from the "front"; (b) the sagittal plane should be regarded as from the "left"; (c) the horizontal (coronal, or transverse) plane should be regarded as from "below."

2. It is suggested that horizontal plane vectorcardiograms should be depicted with their anterior aspect shown at the top of the diagram, viewed as from below.

3. A brief critical review follows. It is again pointed out that some authors' conventions are not consistent with those laid down by Einthoven, which should not now be abandoned after so long a period of time.

Dr. Wallace Brigden has given valuable constructive criticism, and his help is gratefully acknowledged. It is a pleasure, also, to thank T. G. Ward, one of whose technicians, L. Yeates, kindly made the "perspex" models used for Figs. 1 and 2.

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PAROXYSMAL PSEUDOVENTRICULAR TACHYCARDIA AND
PSEUDOVENTRICULAR FIBRILLATION IN PATIENTS
WITH ACCELERATED A-V CONDUCTION

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THE sudden development of a very high grade tachycardia associated with palpitation and giddiness and sometimes weakness and visual disturbances, vertigo, and even syncope, calls for prompt electrocardiographic study. In the patients that we are about to discuss in this report, the electrocardiograms taken during the attacks alarmed the residents and electrocardiographers. The rapid succession of what appeared to be ventricular complexes, uniform or varying, presented the appearance of serious paroxysmal ventricular disorders.

In spite of these apparently ominous electrocardiographic tracings, the physician is reassured if he can still feel the pulse and when he finds that the blood pressure is fairly well maintained. An extremely high ventricular rate, with regular or irregular rhythm, should give the clue to the possibility that one is dealing with an atrial tachycardia or an atrial fibrillation in a patient with accelerated A-V conduction and false bundle branch block. These are prone to atrial paroxysms,^{1-3,5-7,10-13,16-18} and so a pseudoventricular mechanism is suggested. The same electrocardiographic pictures could be produced by paroxysmal atrial tachycardia or fibrillation in one with true bundle branch block, but generally the rates would not be so high. Electrocardiograms taken after the episodes usually show the characteristic short P-R intervals and slurred-up R delta waves of the Wilson, Wolff, Parkinson, and White syndrome³ or the aberrant Bundle of Kent syndrome of Wood and Wolferth,^{4,7} and the accelerated A-V conduction and false bundle branch block of Wolff¹⁷ and Prinzmetal.¹⁴

We have had the experience of witnessing the inscription of the ECG in two pseudoventricular tachycardias and four of the pseudoventricular fibrillation disorders in six patients. We have accomplished prompt conversion to sinoatrial rhythm in all of them, occasionally by simple but usually only after heroic therapy with intravenous procaine amide. The electrocardiograms in each of these patients after the attacks showed the so-called WWPW syndrome of short P-R interval and slurred up R delta waves, slightly broad QRS complexes of at least 0.10 second duration in the standard leads and in the precordial leads.

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CASE REPORTS: PAROXYSMAL ATRIAL TACHYCARDIA WITH FALSE
BUNDLE BRANCH BLOCK

CASE 1.—L. L., a school-girl patient of Dr. J. L. Knighton, had her first attack of rapid heart action at age 11 in August, 1949. She felt rapid forceful palpitation, extreme weakness and giddiness, and tightness in the chest. She slumped but did not lose consciousness completely or at the most only momentarily. The ECG was thought to be paroxysmal ventricular tachycardia with an unusually high rate of 280. It was, however, pseudoventricular, actually atrial tachycardia with false bundle branch block as shown in Fig. 1. She had always been in good health and had led an active life. Physical examination revealed no abnormalities except the tachycardia and low blood pressure. After sedatives and vomiting the episode stopped and the postparoxysmal ECG showed accelerated A-V conduction.

In the second attack which accompanied a respiratory infection in January, 1950, she was extremely weak, pallid, cyanotic, and in shock. Her blood pressure was 88/80 mm. Hg during nausea and vomiting. The rapid heart action was refractory to carotid sinus pressure, sedatives, quinidine, and digitoxin given parenterally. Quinidine, 0.2 Gm., was continued orally every three hours and the attack lasted twenty-six hours. Fever and râles in the lungs persisted for several days. In the third attack in March, 1950, Phenobarbital sodium parenterally and quinidine orally were ineffectual, and after seven hours procaine amide or Pronestyl, 250 mg. intramuscularly, seemingly stopped the attack. The fourth attack in June, 1950, came while she was swimming in a pool and subsided spontaneously. The fifth attack in February, 1951, stopped in a minute or so after the injection, intravenously, of 250 mg. of Pronestyl.

In the sixth attack in December, 1951, the patient, then 13 years old, was treated with two intravenous injections, a total of 500 mg. of Pronestyl, within thirty minutes. There was no definite slowing but alternation appeared in the ECG three hours later and the paroxysm stopped. Pronestyl, 250 mg. every three hours, was continued for occasional premature contractions, which had been noted preceding attacks. These were usually controlled with Pronestyl, 250 mg. by mouth every three hours.

The attacks had been most frequent and severe during the first year of her menarche. Premonitory symptoms and premature contractions were noted and were promptly erased. Attacks decreased in number as the patient's emotional stability increased during adolescence. She was seen at the age of 18 years and stated that she had been free of attacks for three years.

CASE 2.—R. B., a 16-year-old boy, complained of attacks of rapid heart action, generalized weakness, nausea, and vomiting. These episodes had recurred every two months for six years and had lasted from two to twenty-four hours. The paroxysms stopped spontaneously as a rule after an hour or so and only rarely lasted longer. On physical examination there was pallor, especially marked during the attack, and his blood pressure dropped to 100/70 mm. Hg. Heart action during the attack was forceful with a systolic thrill and a loud, slightly rough, Grade 3 blowing systolic murmur heard at maximum intensity in the third and fourth left intercostal spaces at the sternal border and transmitted toward the tricuspid area. These findings were considered to be those of an interventricular septal defect. There were no evidences of heart failure, no orthopnea or dyspnea, and no engorgement of the liver or edema were noted.

ECG's during the attacks, taken by Dr. Pat McKay, showed ventricular complexes at the rate of 230 per minute as shown in Fig. 2. However, definite P waves could be identified on each complex indicating a supraventricular tachycardia. ECG after the attacks showed typical short P-R intervals, slurred-up R and delta waves, and compensatory broad QRS intervals.

CASE 3.—Mrs. D. F. V., a housewife, aged 31 years, and mother of three children, complained of short, rapid, irregular heart action almost daily. She had had episodes of this type all of her life. The attacks had gradually become more severe. She had a severe attack in January, 1954, collapsed with extreme weakness and shortness of breath, and had noted palpitation and irregular heart action. Carotid sinus massage had been ineffectual. She had been put under an oxygen tent and digitalized. Her heart action was irregular, 185 to 210 per minute. Her blood pressure was 90/80 mm. Hg. The attack lasted for forty-eight hours and she was hospitalized for several weeks. The ECG, Fig. 3, was interpreted as showing ventricular fibrillation.

In another severe attack, in 1954, she also suffered pain in the precordium, which radiated through to the back. The rapid, irregular heart action was counted at 210 per minute and the blood pressure was 100/80 mm. Hg. Her B. M. R. was found to be high and she was put on anti-thyroid drug. She had been drinking two to three cups of coffee and smoking a package of cigarettes a day. These were discontinued.

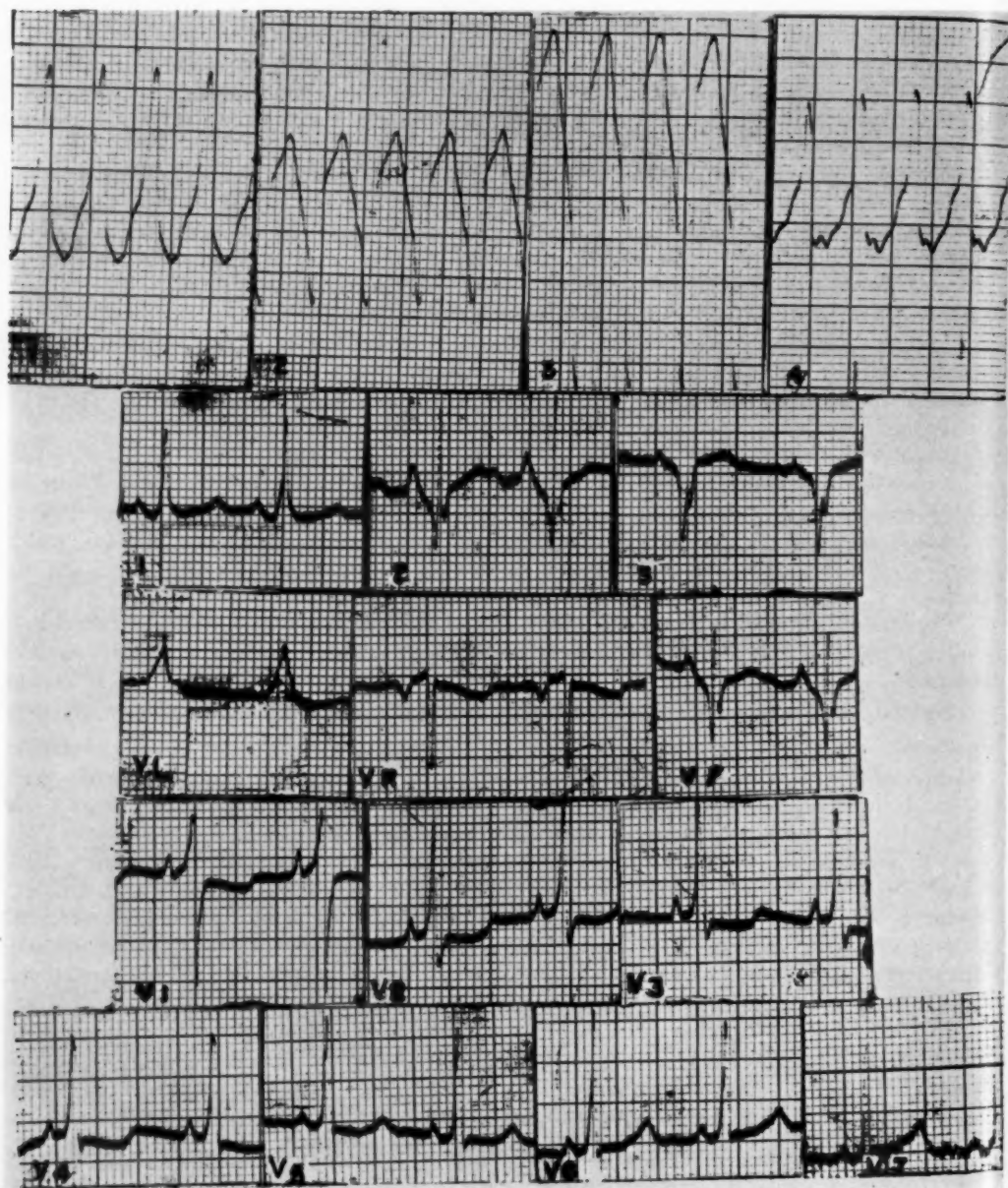


Fig. 1.—L. L., 12-year-old white school girl, P. P. No. 3112, showing a pseudoventricular tachycardia at top in standard Leads I, II, III, and IV. Note P-wave notch on each complex, especially in the negative T of Lead $\frac{1}{2}$. Below, the routine 12 leads showing sinoatrial rhythm with WWPW syndrome after Pronestyl injection.

Physical examination showed no abnormality after the attack was over. The heart was not enlarged, and no abnormal sounds were heard. Blood pressure was maintained at about 110/64 mm. Hg.

Fig. 3, taken during the attack, showed very irregular heart action and various bizarre types of ventricular complexes. The occasionally short runs of narrow QRS complexes and no P waves justified the diagnosis of supraventricular atrial fibrillation, pseudo bundle branch block and pseudoventricular fibrillation of accelerated A-V conduction. The ECG after the attack showed accelerated A-V conduction and slurred-up R delta waves, and broad QRS complexes.

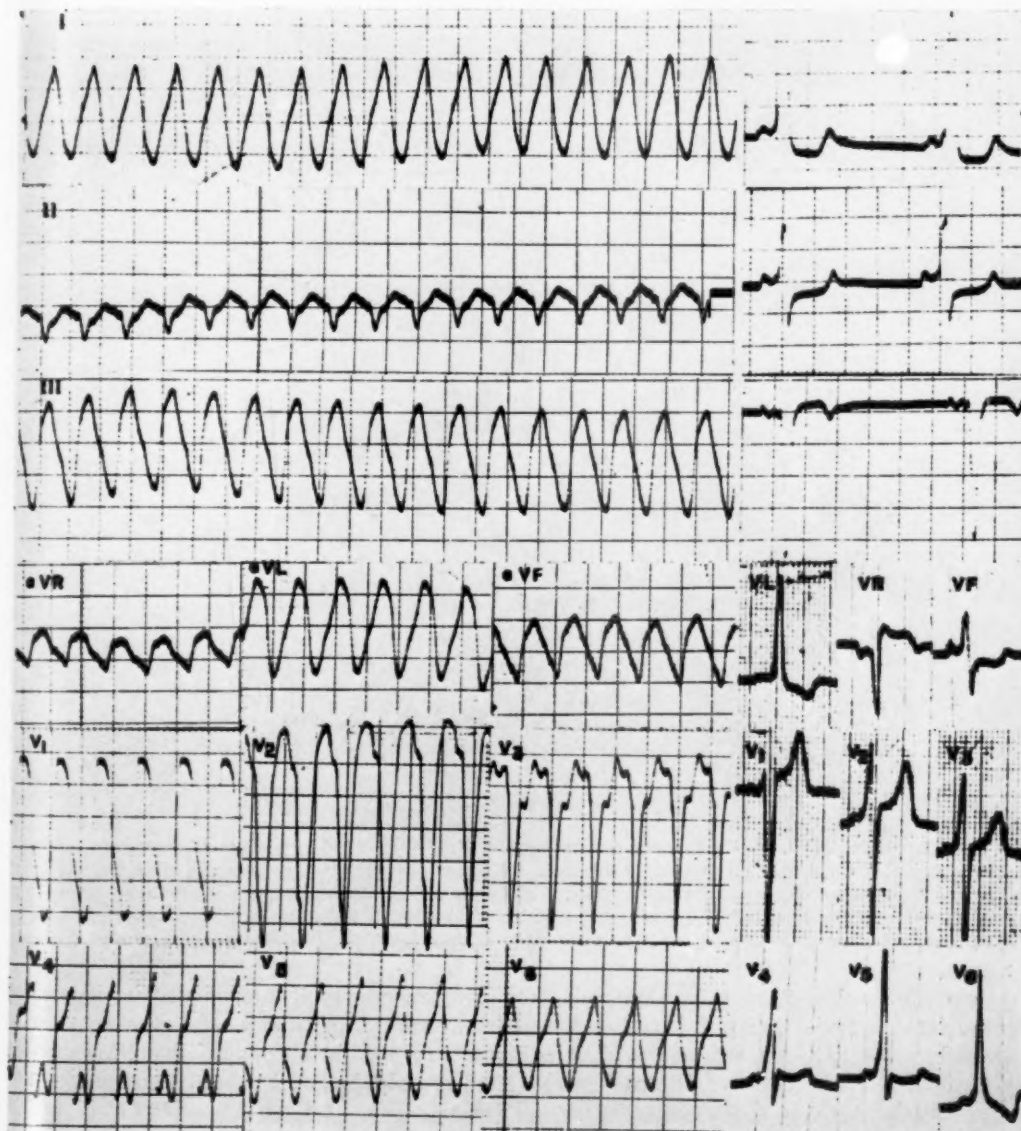


Fig. 2.—R. B., 16-year-old white man showing pseudoventricular tachycardia. Note the absolute regularity. In certain leads, notches, probably P wave, occur at the same place in each broad QRS complex. On the right side of the figure are the standard leads taken during normal sinoatrial rhythm with accelerated conduction of WWPW syndrome.

CASE 4.—G. S., a 32-year-old man, was perfectly well until Jan. 10, 1952, when he suddenly collapsed after a venesection. The attending physician reported that he could not feel a pulse, nor get a blood pressure, nor hear a heart sound.

ECG's (Fig. 4) taken within thirty minutes seemed to confirm the diagnosis of ventricular fibrillation. The situation was considered quite grave. However, the patient seemed to be improving somewhat on lying in bed. The irregular heart action was 230 per minute and the blood pressure was 80/70 mm. Hg, but the rapid irregular heart rate persisted.

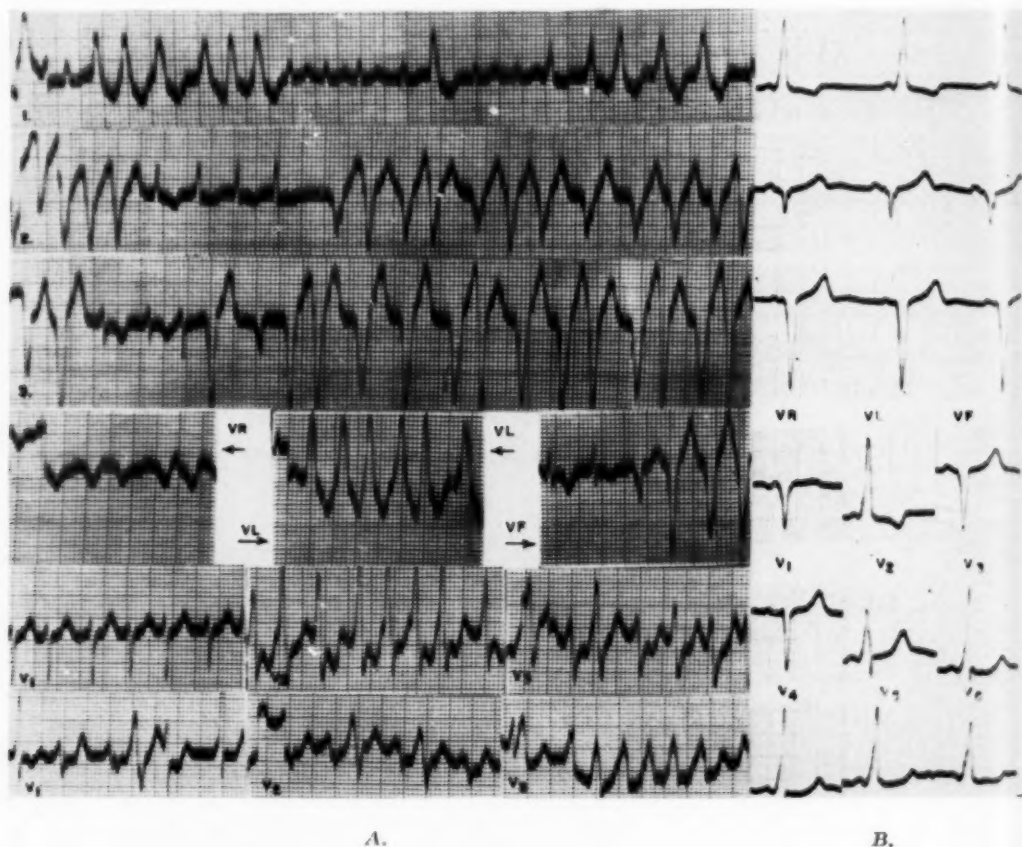


Fig. 3.—ECG of D. F. V., 32-year-old housewife, P. P. No. 3766. A, during paroxysm. All 12 leads after showing pseudoventricular fibrillation. B, After paroxysm. All 12 leads after digitalis and quinidine showing accelerated conduction of WWPW syndrome. Note that the mechanism producing the aberrant ventricular type QRS during the paroxysms is interrupted occasionally by supraventricular narrow QRS complexes without P waves showing the underlying atrial fibrillation at intervals.

Procaine amide, 500 mg. intravenously, was given and the patient responded satisfactorily, as the rapid irregular heart action was soon under control. After the normal mechanism was established, the ECG showed typical short P-R intervals and the slurred-up R delta waves of accelerated A-V conduction. The patient recovered completely and had no recurrences of the paroxysm.

CASE 5.—A. G. B., a veteran, aged 26, complained of irregular pounding of the heart which came on after returning from a fishing trip. He felt a heaviness in the chest, giddiness, and some weakness. Pulses were barely palpable, very irregular, and were difficult to count. Precordial auscultation of his heart revealed rapid and irregular heart action at a rate of more than 200 per minute. The blood pressure, however, was maintained at 110 mm. Hg systolic and 55 mm. Hg diastolic.

Fig. 5, taken in the John Sealy Hospital emergency room was interpreted as showing ventricular fibrillation, at a rate of 220 to 240 per minute. The blood pressure was 106/60 mm. Hg. The patient did not seem to be in the extreme state that the ECG suggested. Carotid sinus pressure was ineffectual.

Procaine amide, 1000 mg. intravenously, decreased and eliminated the aberrant appearing complexes which obviously were due to atrial supraventricular fibrillation and bundle branch block.

ECG taken after regular rhythm showed the heart rate to be 78 with the short P-R interval and slurred-up R delta waves of accelerated A-V conduction.

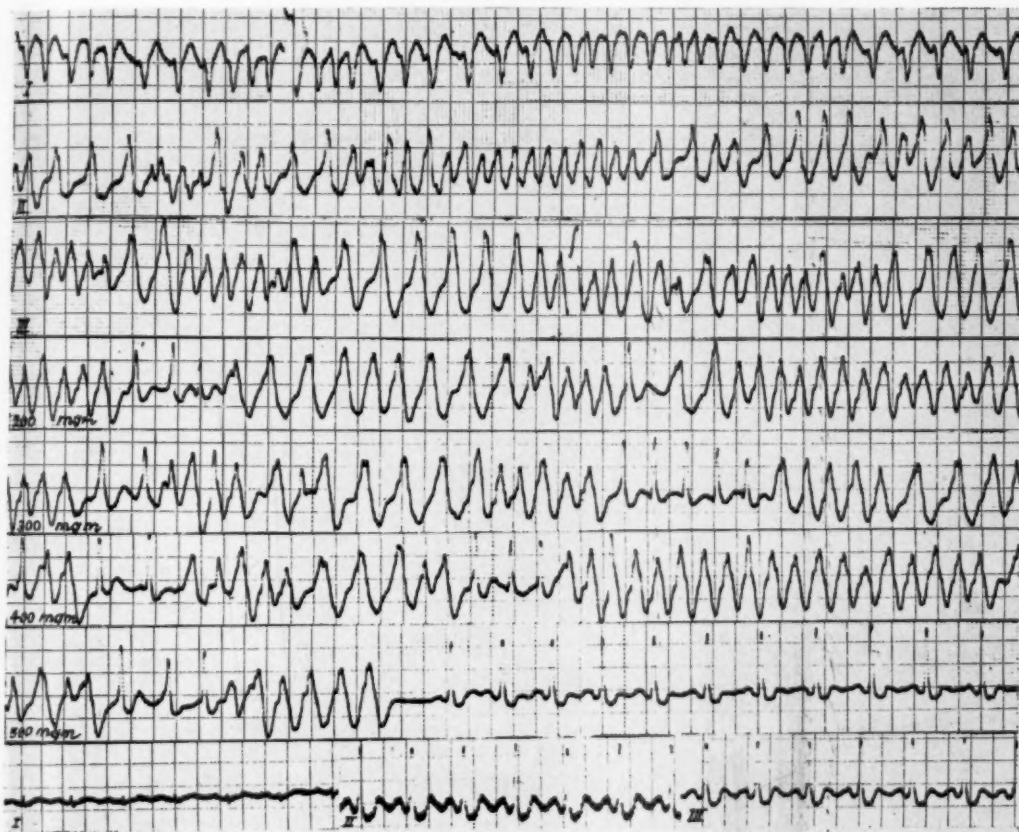


Fig. 4.—ECG of G. S., 40-year-old blood donor showing pseudoventricular fibrillation at a rate of 285 per minute. Standard Leads I, II, and III across the top of the figure following these are portions of Lead II, during increasing dosage of Pronestyl. At the bottom, standard Leads I, II, and III after the paroxysm has been interrupted and normal sinoauricular rhythm with WWPW syndrome.

CASE 6.—J. R., aged 22, Pfc, USMC, a patient of Drs. Thomas M. Runge, R. P. Martin, and M. H. Levin, had an attack of irregular palpitation while playing baseball. A slight substernal discomfort and slight faintness developed. He stated that he had had similar episodes since the age of 8 years and under conditions of stress.

He walked into the hospital. His peripheral pulses were barely palpable but present. His heart action was audible but too rapid and irregular to count. The blood pressure was maintained at 100/70 mm. Hg.

The ECG (Fig. 6) showed rapidly recurring bizarre variable QRS complexes at rates of 240 to 280 per minute. A diagnosis of "Chaotic Heart Action" was made. The suggested diagnosis of ventricular fibrillation was ruled out because of the maintenance of peripheral pulses and blood pressure and the absence of signs of collapse and the presence of heart sounds.

Emergency therapy of Pronestyl was given in doses of 0.5 Gm. intramuscularly and 0.5 Gm. intravenously. This slowed the ventricular rate to 150 per minute and the ECG showed short runs of narrow ventricular complexes and atrial fibrillation.

Morphine sulfate, 16 mg. subcutaneously, and Seconal, 0.1 Gm. every four hours, and Pronestyl, 0.5 Gm. intravenously at the fifteenth hour, resulted in nausea and vomiting. At twenty hours the pulse became slower and regular.

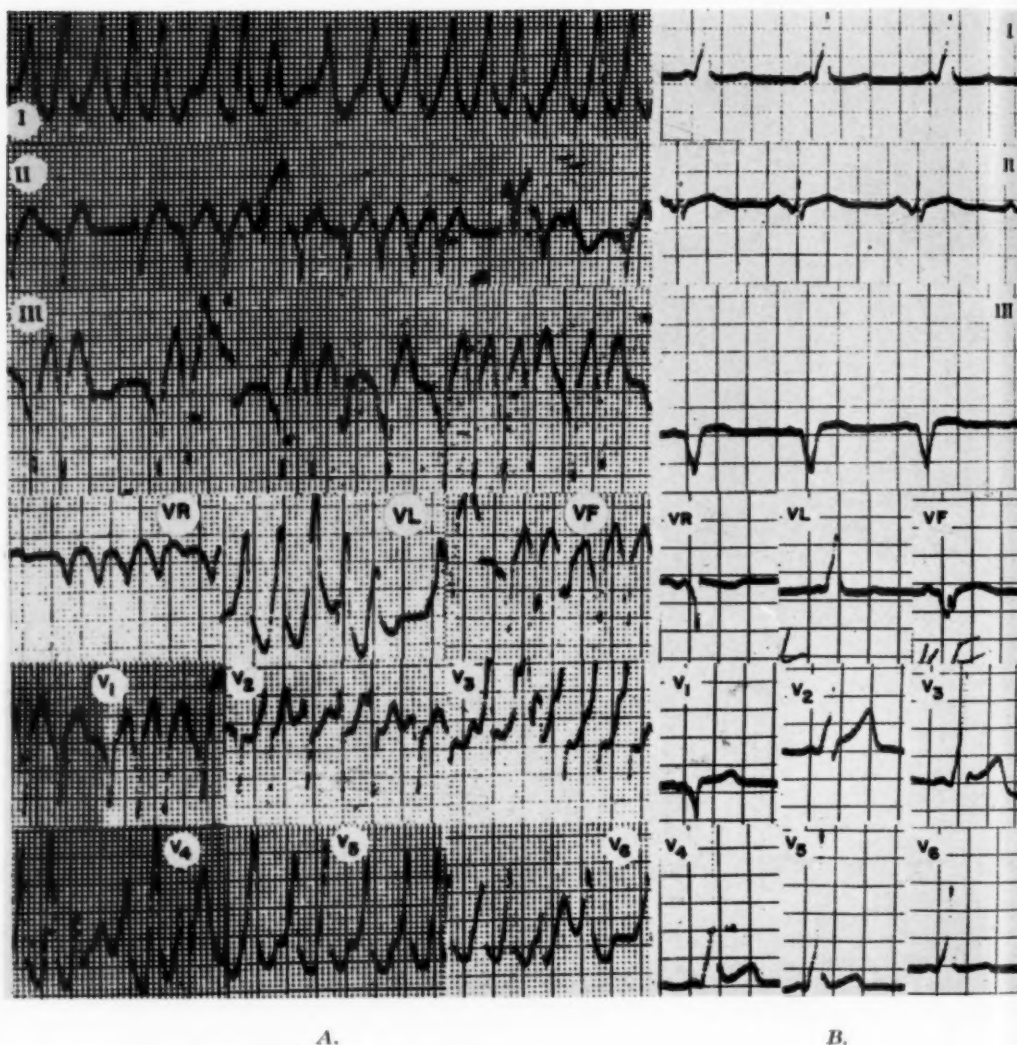


Fig. 5.—ECG of A. G. B., 26-year-old white veteran, showing pseudoventricular fibrillation. A, During paroxysm. Pronestyl produced reversed at first to supraventricular typical atrial fibrillation the underlying paroxysm. Later (B), after paroxysm, normal sinoauricular rhythm with WWPW syndrome was traced.

The ECG (Fig. 6) taken after the attack showed sinoatrial arrhythmia and accelerated A-V conduction and slurred-up R delta waves. He was maintained on quinidine, 0.1 Gm. every four hours.

DISCUSSION OF THE DIAGNOSTIC CRITERIA AND PROGNOSIS

Extremely rapid heart action, regular or irregular, over 200 per minute, suggests strongly the presence of accelerated A-V conduction with paroxysmal atrial tachycardia or fibrillation. Pseudoventricular tachycardia and pseudo-

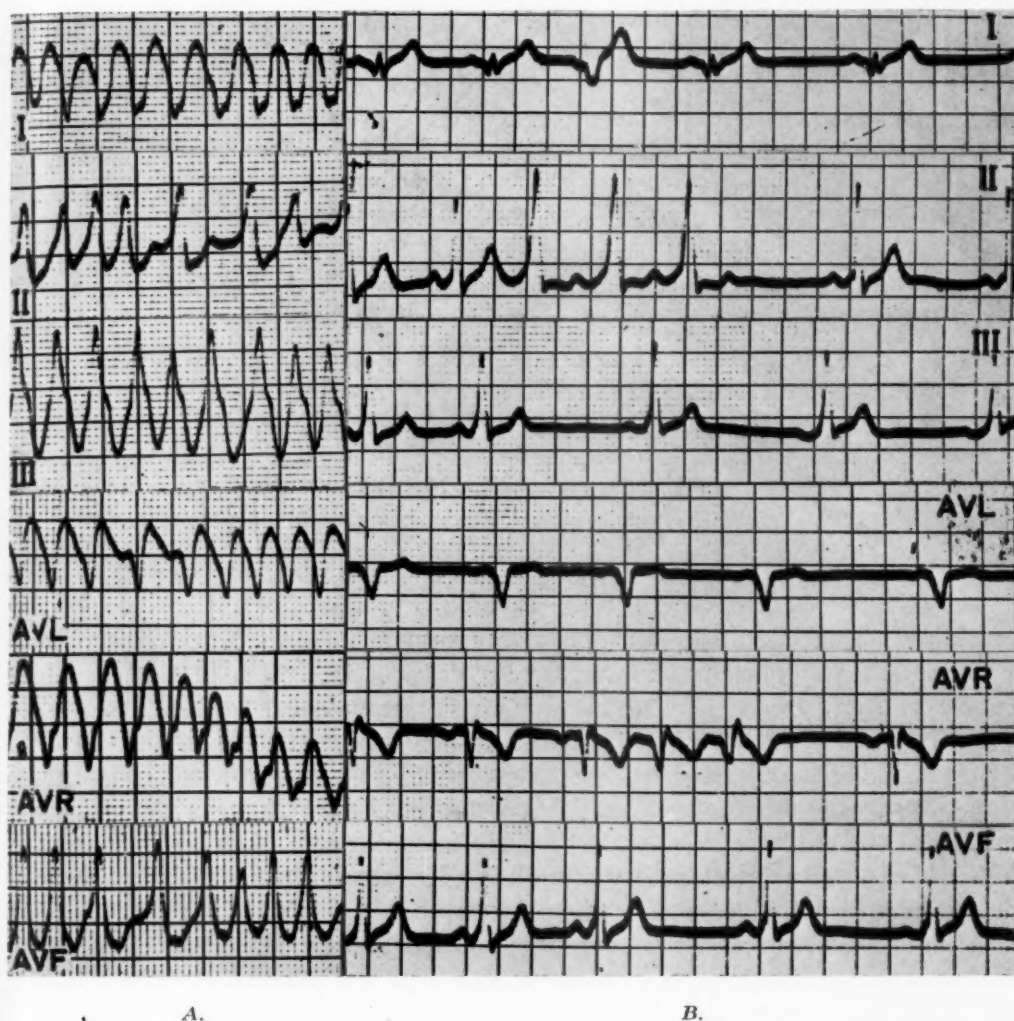


Fig. 6.—J. E. R., 20-year-old marine. A, All leads during paroxysm showed pseudoventricular fibrillation. Only 6 standard leads, I, II, III, aVL, aVR, and aVF, were mounted. B, Six leads after giving 1 Gm. Pronestylol: 0.5 Gm. intravenously and 0.5 Gm. intramuscularly. Note that aberrant QRS complexes of three premature atrial beats in II are exactly the same as those recorded in A and in aVF, short P-R and slurred-up R delta waves.

ventricular fibrillation are regular or irregular and usually of higher rates than the true ventricular types and the patient's condition is far less serious. The clinical picture in spite of bizarre and ominous looking electrocardiograms portends, as a rule, a more favorable prognosis. The presence of visible and palpable peripheral pulses and audible heart sounds and the maintenance of blood pressure are reassuring as well as differentially diagnostic signs.

In the electrocardiogram the presence of a high grade of tachycardia of regular rhythm with false bundle branch block complexes and regularly placed P waves on each broad QRS, and occasionally a few narrow complexes, are diagnostic criteria of paroxysmal pseudoventricular tachycardia. A paroxysm of an absolutely irregular rhythm with no P waves and occasionally short runs of narrow QRS intervals and very high ventricular rates of over 200 indicates atrial fibrillation with false bundle branch block or pseudoventricular fibrillation of the WWPW syndrome. Occasionally in these same types of patients the paroxysms may show narrow ventricular complexes and no abnormal forms. Every paroxysm that we have studied has been supraventricular in origin. There is no established explanation for the frequency of either of these two types of paroxysms in patients with accelerated conduction.

The prognosis is generally good but in a rare case the patient has died in an attack.^{7,9} The postparoxysmal findings are characteristic. There is short P-R interval, less than 0.12 second, and the slurred-up R delta wave on the upstroke of R, and the compensatory broadened QRS and often oppositely directed T waves confirm the diagnosis. Prompt recognition of the disorders is possible from the clinical findings and confirmed by electrocardiograms.

THEORETICAL CONSIDERATIONS

The pathogenesis of the electrocardiographic pattern of a short P-R interval, slurred upstroke of R, the delta wave, and a compensatory broadening of QRS is generally conceded to be due to accelerated conduction of the cardiac excitatory impulse from the atria to a part of the ventricular muscle which is prematurely activated. This is theoretically accomplished through (a) an accessory Bundle of Kent^{3,4} or (b) by a decrease in the normal delay of conduction that occurs in parts of the pathway or in the normal atrioventricular node.^{8,14}

Sodi-Pallares and associates¹¹ concept is based on the experimental findings of one hyperexcitable focus in the I-V septum near the pulmonary valve A and another near the tricuspid valve B. French cardiologists¹¹ reported an autopsied WWPW case with an accessory Bundle of Kent ending in one of these foci. This results in interference of a sinoatrial rhythm with a rhythm of the heterotopic high interventricular septal focus. The slurred upstroke of the R, the delta waves, are due to early activation of the hyperirritable point A or B in the right interventricular septum.

Prinzmetal and associates feel that it is not necessary to postulate the accessory pathways but instead consider the presence of irritable A-V nodal and bundle fibers that conduct impulses at supernormal speeds.

After the ventricle is prematurely activated the excitatory process enters the ventricular conduction pathways and spreads in accordance with its position directly just as does a ventricular ectopic beat. The ventricular complexes at slow rates are deformed independently of sinoauricular activation. Abnormal ventricular complexes persists in cases of nodal rhythm and A-V block and are exaggerated usually in paroxysmal atrial tachycardia, flutter, or fibrillation. The normal A-V pathways are refractory to rates above 240 and particularly of atrial fibrillation impulses which would rarely be conducted rapidly enough

to produce irregular ventricular rhythms of the high rates recorded. An irregular ventricular rhythm of 240 rate, therefore, practically designates the presence of accelerated conduction of the WWPW type. Supraventricular disorders are conducted rapidly through the same aberrant pathways. An intraventricular origin of these rapid paroxysmal rhythms in WWPW syndromes would be impossible otherwise.

TREATMENT

Procaine amide (Pronestyl) in 0.25 to 1.0 Gm. doses intravenously, up to 2 Gm. in twenty-four hours seems to us to be the drug of choice. It should be given slowly, intravenously, with constant electrocardiographic monitoring and frequent blood pressure readings as advocated for all interventricular therapy for high-grade cardiac mechanism disorders. The drug is stopped after conversion of the disorder has been accomplished or when toxic broadening of the QRS interval increases above 25 per cent of its original duration or if the blood pressure suddenly drops to significantly lower levels.

Quinidine sulphate would seem to be the drug of choice for supraventricular arrhythmias, particularly fibrillation. However, it is probably somewhat more dangerous when given intravenously even with monitoring and has caused cardiac standstill.

Both Pronestyl and quinidine drugs given intravenously may cause equally serious drops in blood pressure and must then be stopped at least temporarily.

If Pronestyl fails quinidine should be started by mouth in 0.2 Gm. doses hourly. Unfortunately, these patients often seem to be intolerant of quinidine by mouth during paroxysms. If intolerance symptoms appear with one drug the other should be tried. Quinidine is usually well tolerated and fairly effective and preferable as a prophylactic between attacks because procaine amide has more of a tendency to produce sensitization reactions.

Digitalis preparations were used in some of our cases with questionable effects in one case of pseudoventricular paroxysmal tachycardia. It has rarely been found effective, even in lowering the ventricular rate in pseudoventricular paroxysmal fibrillation of atrial fibrillation origin. Increasing the dosage of digitalis in an attempt to slow the ventricles may result in intoxication and may increase the ventricular irritability seriously.

SUMMARY

Patients with accelerated atrioventricular conduction are peculiarly prone to paroxysmal atrial tachycardia and atrial fibrillation, which with the conduction anomaly result in very rapid arrhythmias, producing bizarre electrocardiograms.

The pseudo bundle branch block causes the development of pseudoventricular complexes and the accelerated atrioventricular conduction gives rise to high ventricular rates that are alarming. These are usually more rapid than the simulated serious ventricular mechanism disorders.

The importance of taking the seemingly good general status of the patient into consideration in electrocardiographic interpretation is emphasized.

The diagnostic criteria have been set forth with emphasis on the presence of a P wave on every complex in the tachycardia and short runs of definite supraventricular fibrillation with narrow QRS in between the bizarre pseudoventricular runs of complexes. Some of the cases of a paroxysmal ventricular tachycardia and some of the cases of paroxysmal ventricular fibrillation with recovery reported in the literature are probably of this pseudoventricular disorder.

The relatively excellent prognosis of the pseudo type is emphasized. However, it must be remembered that, in a rare case, the patient has died suddenly in a paroxysm of tachycardia. The relatively prompt and satisfactory response to procaine amide intravenously has been demonstrated. Some patients seem to be somewhat refractory to quinidine during a paroxysm and digitalization does not effectively slow the ventricular rate in this type of atrial fibrillation and accelerated conduction.

The probable pathophysiology of these pseudoventricular paroxysms, tachycardia, or fibrillation have been discussed. The conspicuously high ventricular rates are the result of the accelerated A-V transmission.

The clinical axiom follows that the presence of ventricular paroxysmal disorders, regular or irregular, with rates above 240 is presumptive evidence of the presence of accelerated A-V conduction as the fundamental cardiac mechanism disorder in the patient.

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CONTROL OF BODY FLUID VOLUME

SOME OBSERVATIONS AND A HYPOTHESIS

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HENDERSON¹³ considered the regulation of body volume to be perhaps the most universal and fundamental of all biologic regulations. In the mature individual this regulation is largely of fluid, for this represents some 70 per cent of the total lean body substance. However, despite a great deal of investigation, considerable uncertainty remains concerning the mechanisms by which the body fluid volume is regulated.

It is the purpose of this paper to review observations made at this Center concerning the regulation of body fluid volume and to propose a hypothesis which unifies these observations. This hypothesis is based on the concept of "open" systems which figure largely in other branches of science from astronomy to microbiology.

INTRODUCTION

The body fluids are essentially solutions of electrolytes (solutes) in water (solvent). Although the absolute volume of the solutes is small compared with that of the solvent, they have been shown to influence the volume of fluid in the body. Of the many properties of the various electrolytes it is their additive property—osmotic pressure—which exercises this influence.

Basically the body may be regarded as a store of fluid which has a continuous inflow and outflow. That these flows are continuous is self-evident for, although fluid may be drunk intermittently, the fluid supplied by metabolism and the formation of urine are continuous processes. For the present discussion it is assumed that fluid lost by routes other than the kidney is used for temperature regulation purposes and represents a load on the volume-regulating system (Peters²⁴).

Our observations concern fluid intake, fluid output, and body fluid volume changes in normal adult man and rabbits (Fowler^{6,7}), and in a variety of clinical states in man in which there has been disturbance of body fluid volume (Lowe^{16-19,22} Lowe and Sayers,²³ Fraser and Lowe,⁸ and Hamilton,¹¹). These conditions include edema due to various types of cardiac and renal disease and also endocrine disturbances.

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We have shown that, under standardized conditions of daily diet (with caloric, electrolyte, and fluid content controlled), of ambient temperature, and of observational procedures, the fluid drunk and urine output each twenty-four hours are reliable indices of changes in total intake and output of fluids (Lowe¹⁷).

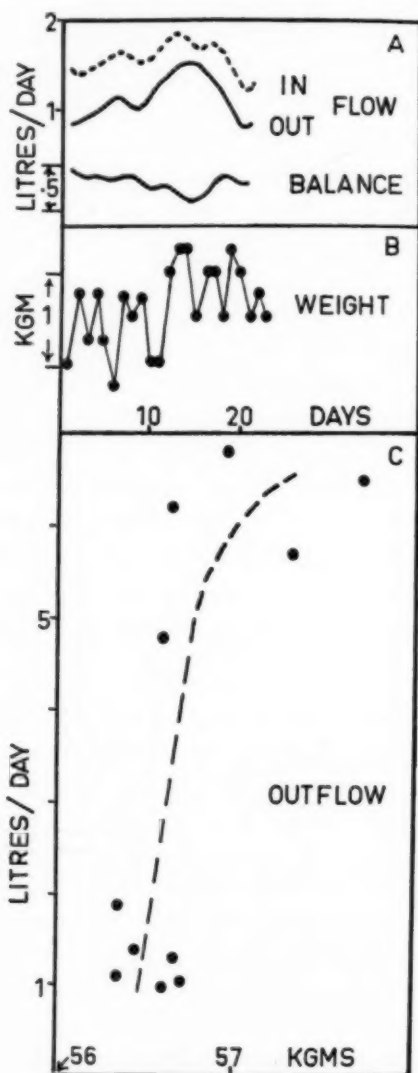


Fig. 1.—Data from three normal patients (A, B, and C) obtained under standard conditions recording from A the daily fluid intake and output, as defined in text, and the difference of these (balance), from B the daily body weight, and from C the daily fluid output plotted against body weight (volume index).

Also daily weight changes are a good index of the changes in body fluid volume (Fowler⁶). The difference between intake and output gives a daily fluid balance which agrees with the observed weight changes.

In all, the fluid intake, fluid output, and changes in body fluid volume and daily weight, as defined, have been recorded in a series of 265 patients. In addition similar observations have been made on a number of adult rabbits.

OBSERVATIONS

Normal Adult.—The daily intake and output of fluid and weight fluctuate in magnitude and when plotted against time yield curves similar to those of Fig. 1, A and B. Fluctuations of the intake and output curves are largely in step and of similar magnitude so that they run nearly, but not quite, parallel. This leads to variations in the daily fluid balance, which are reflected in the weight curve and which give an indication of the degree of control of body fluid volume

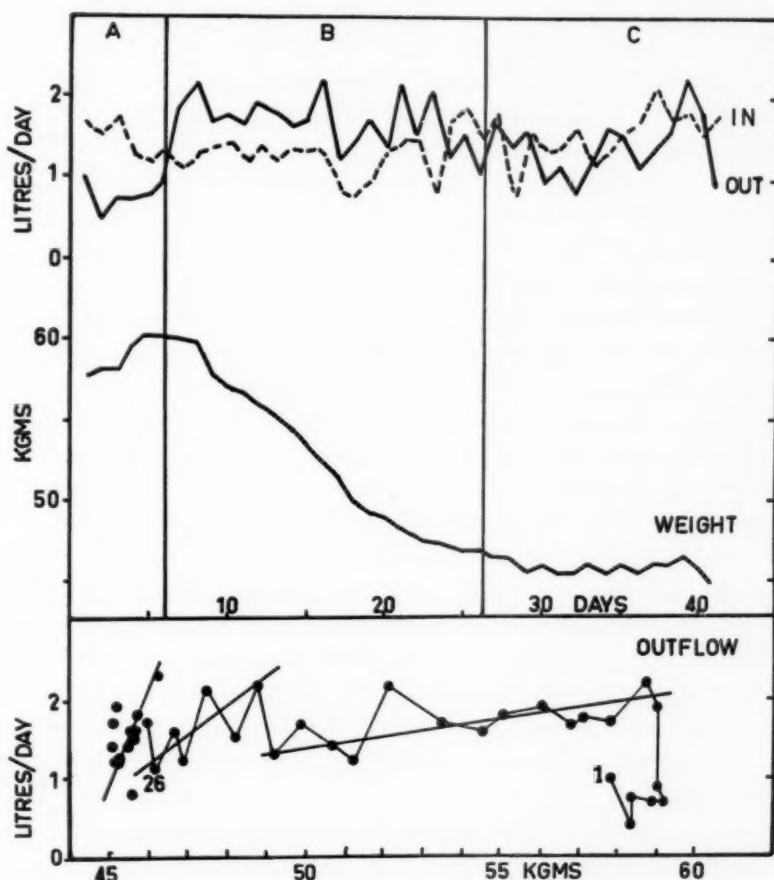


Fig. 2.—Data obtained from a patient recovering from congestive cardiac failure. In the upper section the daily fluid intake and output and daily body weight are plotted. A, B, and C indicate the three sections discussed in the text. In the lower section the daily fluid output is plotted against body weight. The numbers 1 and 26 indicate the day of observation, and the lines joining the dots indicate the progression of the observations. The three sloping lines drawn through the dots indicate approximate linearity in those regions.

and indicate that regulation in man can be as accurate as ± 500 ml., which is equivalent to ± 0.5 kilogram body weight, over considerable periods. The fluctuations seen in all the curves appear to be haphazard.

When the daily output of fluid is plotted against body weight (Fig. 1, C) the relationship is probably represented by a sigmoid curve, the center part of which is virtually linear. Small changes in volume produce big changes in flow in the center linear part of the curve.

Edema States.—A considerable proportion of patients suffering from congestive cardiac failure will lose their edema if confined to bed. Observations of intake, output, and body weight were made on such patients under the standard conditions in the belief that they would represent the natural behavior of the body in recovery from a condition of excess fluid storage unaffected by any but the simplest therapeutic measures. In others the effects of various therapeutic agents for relieving the edema of congestive cardiac failure were studied.

The changes in inflow, outflow, and body weight were also observed both during the development of and recovery from edema produced by other causes.

Study of the intake, outflow, and body weight curves indicates that in most instances the recovery period can be divided into three parts (Fig. 2, A to C).

Changes in Body Volume.—In patients suffering from congestive cardiac failure, and losing edema naturally, the body volume, as indicated by body weight, follows a pattern reproducible from patient to patient and also in the same patient on different occasions. The recovery period can be divided into three sections (Fig. 2).

The first section (Fig. 2,A), often well defined but sometimes absent, shows either a slow fall or, in some patients, a small gain in volume which corresponds to a small but increasing negative fluid balance or, in those patients showing a weight gain, a diminishing positive balance. This phase lasts only a few days.

The second section (Fig. 2,B), which constitutes the bulk of the recovery period, consists of an accelerating and then slowing weight loss. The fluid balance is negative throughout this period, increasing to a maximum and then diminishing toward zero. This period lasts up to two weeks.

The third section (Fig. 2,C), consists of fluctuations of the weight about a mean level and small fluctuations of the daily fluid balance about the balance line. These fluctuations are sometimes regular, but more often haphazard, and are of somewhat greater magnitude than those of normal individuals.

When the graphs are smoothed the curves indicate clearly the underlying trends unobscured by the random day-to-day fluctuations. The fluid balance curves (derived either from intake and output or from the body weight) are complex sine waves.

In the natural recovery from edema states due to other causes, such as acute nephritis and the nephrotic syndrome, the body volume undergoes qualitatively similar changes. In the development of edema this picture is seen in reverse.

When recovery from edema states is brought about by potent diuretic agents the body's behavior is best demonstrated in the fluid balance curves. It is then seen that the resulting change depends on the phase of the balance curve at the time of administration. If the curve is in a positive retention phase, frequently it is abruptly changed to a negative loss phase and then continues its cyclic course. If it is in a negative phase then this loss is merely accentuated.

Changes in Inflow and Outflow.—The three sections already mentioned can be discerned in the changes in inflow and outflow of patients recovering naturally from edema states (Fig. 2).

In the first section, however, two general behavior patterns are noted. In one the direction of change of inflow and outflow with time is opposite; as

one increases the other decreases. In the other pattern both inflow and outflow move in the same direction, with the outflow increasing much more than the inflow. When these changes are compared with the weight changes, it is found that in those patients with an initial weight gain the inflow and outflow curves always move in opposite directions, with the inflow greater than outflow.

In the second section the inflow and outflow curves move roughly parallel, but with outflow greater than inflow.

In the third section the inflow and outflow behavior is substantially that of the normal individual.

The exhibition of various diuretic agents usually results in sudden increases in the daily output of fluid, with little or no change in the intake.

In a number of the patients it was possible to show that the relationship between daily outflow of fluid and body volume (body weight) could be represented by a straight line, and that in the course of recovery there were often sudden shifts to higher levels of outflow function. These shifts are sometimes spontaneous, sometimes therapeutically induced. In the same way it has been possible to demonstrate depression of this outflow-to-body volume relationship following the exhibition of phenylbutazone and cortisone to patients in normal fluid balance.

In one patient suffering from chronic nephritis the relationship between outflow and body volume could be represented by a sigmoid curve similar to that of the normal individual but with a much smaller slope. This reduction in slope is noticed in all the cases studied in which there is a disturbance of fluid balance.

It was also possible by controlling the level of fluid intake in various patients to show that outflow to volume relationship was independent of the level of intake.

In a number of patients with edema the level of fluid outflow in response to a known intake of water was determined. In all, the outflow was depressed considerably below normal levels but returned toward normal with recovery of the patient.

HYPOTHESIS

As a basis for integrating these observations on the control of body fluid volume it is suggested that the storage of fluid in the body can be represented as an "open" or continuous flow system (Lowe and Sayers,²³ and Lowe²⁰). In such a system there will be continuous inflow and outflow of fluid, and the levels of inflow and outflow are dependent in a reciprocal manner on the volume of storage and the system will be self-regulating (Bartalanffy⁵) with regard to volume. If more than one property of the stored fluid influences inflow and outflow the system will still be self-regulating with regard to volume, but the flow/volume relationships will be more complex. In addition should one or more of these "controlling" properties be dependent on another open system then both open systems must be considered together.

In the present instance we are considering a fluid, consisting of both solvent and solutes, in which both the volume of the fluid and at least one property of its solutes (osmotic pressure) are held within narrow limits. Although the storage of the solutes must be considered as an open system, only the effect of changes in

osmotic pressure on the flow/volume relationships of the solvent need be taken into account when discussing regulation of the solvent volume, for the solute volume is negligible in proportion to that of the solvent.

Evidence that inflow and outflow of fluid in the body are influenced by the fluid volume of the body is provided by the observations of Gilman,¹⁰ Adolph,¹ Barker, Adolph, and Keller,⁴ and Welt and Orloff,³¹ and that they are influenced by the osmotic pressure of some part of those fluids by the work of Gilman,¹⁰ Holmes and Gregersen,¹⁴ and Verney,²⁹ among others.

While in this concept the body is considered as a whole, the internal structure of the storage system is of importance, for the fluid in the body is compartmented into vascular, interstitial, and intracellular spaces, and direct free communication does not exist even within any one compartment. The blood and lymphatic systems provide a transport mechanism which links all these spaces and also connects them with the inflow and outflow points of the body. It is to be expected, therefore, that disturbances in the transport system (Lowe¹⁹) and in the factors controlling the partition of the fluid between the compartments will influence inflow and outflow and the volume of stored fluid.

If the fluid stored within the body influences the inflow and outflow of fluid to the system, then there must exist some mechanism linking the storage with the inflow and outflow points. By analogy with other known controls, there must be some receptor or receptors sensitive to the properties influencing flow and some link between the receptor and the organ which controls the flow. This link could be either nervous or humoral. Verney²⁹ has produced evidence for the existence of a receptor sensitive to osmotic pressure, but only indirect evidence for a "volume" receptor has so far been available (Welt and Orloff,³¹ Gauer and associates,⁹ Viar and associates,³⁰ and Luske and Palmer²⁴). On the effector side of this mechanism, evidence suggests that the hormones of the posterior pituitary gland and the adrenal cortex play a part in the control of the outflow of fluid from the kidney (Leaf and Couter,¹⁵ Verney,²⁹ and Alexander and associates²). Also portions of the brain in the region of the hypothalamus have been shown to be involved in these control pathways, both in regard to inflow and outflow (Nelson and associates,²⁵ Anderson,³ and Greer¹¹).

HYDRAULIC MODEL

To study the behavior of this hypothetical system a number of hydraulic models have been constructed. One model (Lowe²⁰) reproduced qualitatively the disturbances of fluid intake, output, and storage and the osmotic pressure changes observed in the clinical conditions of water and salt loading and deprivation, diabetes insipidus, and the exhibition of posterior pituitary hormone, Addison's disease and Cushing's syndrome, cardiac and nephritic edema, and the action of mercurial diuretics.

This model contained a partitioned fluid storage and both solvent and solute were represented by parallel and linked open systems. A pump-driven circulatory system was incorporated. The outflow valves were complex and had components representative of glomerular filtration and tubular reabsorption. The inflow of solvent was controlled by changes in both the volume and the "osmotic pressure"

of the storage, whereas the intake of solute was controlled only by changes of "osmotic pressure."

The first section of the outflow valves (glomerular filtration) was controlled by changes in the volume of storage, whereas in the second section (tubular reabsorption) the feedbacks of solvent and solute to the system were controlled by change in the osmotic pressure, but in opposite directions.

ANALYSIS OF HYPOTHESIS

Study of the model indicated that its behavior can be represented by a graph of the type shown in Fig. 3. If the "osmotic pressure" is kept constant, then the level of inflow and outflow at particular volumes of storage can be represented by the lines *I* and *O*. These relate the inflow and outflow levels, respectively, to volumes of storage if it is assumed for simplicity that the relationship is linear.

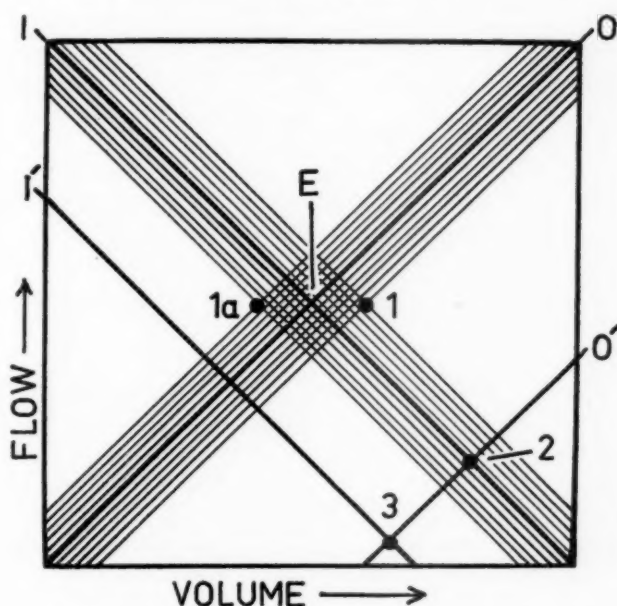


Fig. 3.—Diagram showing changes induced in inflow (*I*) and outflow (*O*) by changes in volume of the hypothetical system. Changes in flow induced by changes in "osmotic pressure" are indicated by the families of lines parallel to *I* and *O* lines. *I'* and *O'* indicate lines of depressed inflow and outflow function. 1, 1a, 2, and 3 indicate abnormal equilibria which are considered in the text.

When "osmotic pressure" is not held constant but is assumed to control inflow and outflow in such a way that a rise in "osmotic pressure" increases inflow and decreases outflow of solvent, then the single lines *I* and *O* become replaced by families of lines. If a three-dimensional model is made, then intersecting planes represent these families of lines.

In this system there will be equilibria or "steady" states in which inflow of solvent equals outflow, and these are represented by the points of intersection of appropriate lines. If in any way, by disease for example, the relationship between flow, volume, and osmotic pressure is quantitatively changed, then other lines, *I'* *O'*, will indicate the relationship and new equilibrium points arise.

This diagram can be used to predict the behavior of the system under a variety of circumstances (Lowe²¹). The resultant behavior can be predicted in terms of flow/volume or flow/time and volume/time relationships. Some of the possible situations are indicated in Fig. 3.

In this figure, E indicates the normal equilibrium point at the intersection of lines I and O . If the inflow/volume relationship is depressed and the outflow/volume relationship elevated, as would occur in a state of lowered osmotic pressure, then $1a$ indicates a new equilibrium point at a somewhat diminished volume. Conversely 1 indicates the equilibrium for a raised osmotic pressure.

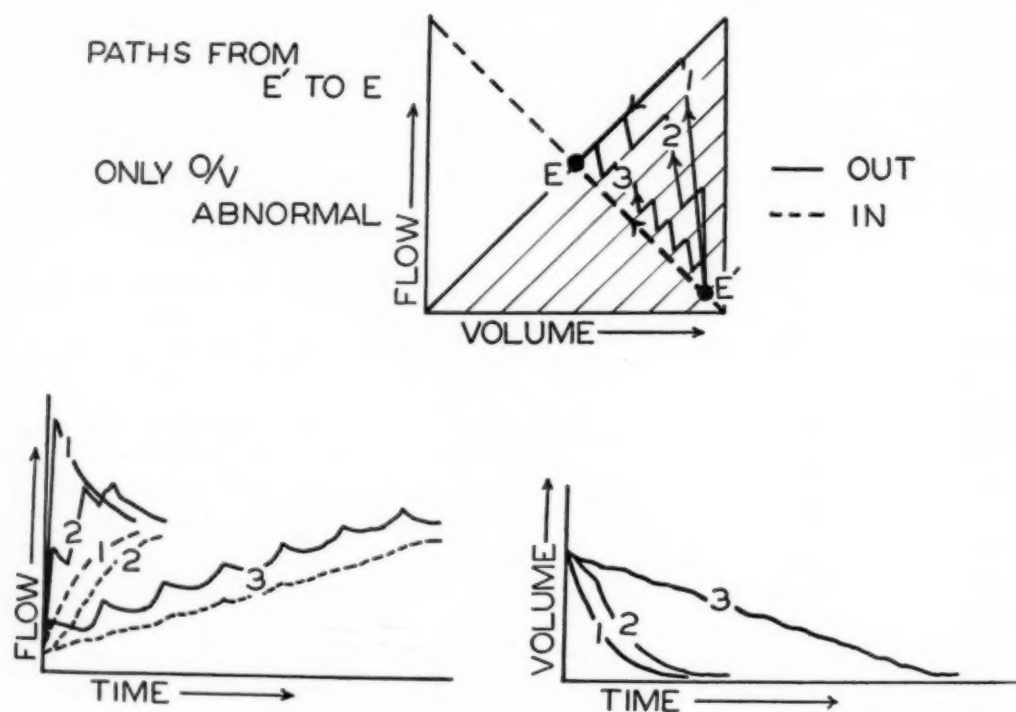


Fig. 4.—Diagram showing, in various ways, recovery pathways of the system from an abnormal equilibrium (E'). In this case only the outflow/volume relationship is abnormal. Path 1 indicates very rapid restoration of O/V relation to normal, paths 2 and 3 indicate stepwise return to normal.

Although points 1 and $1a$ are shown related to E they could occur in association with any other disturbance of the system and could be related, for example, to points 2 or 3.

If the inflow/volume relationship remains normal but the outflow/volume relationship is depressed, then 2 will indicate a new equilibrium at a raised volume. Similarly 3 indicates an equilibrium point when both inflow/volume and outflow/volume relationships are depressed.

While these various disturbances remain constant, the system will remain at one of these equilibrium points, but if the disturbance is removed either rapidly or stepwise, then the system will return to its normal equilibrium point E and the ensuing changes in flow and volume will be indicated by the paths traversed.

In Fig. 4 the recovery from a state of depressed outflow/volume relationship is indicated, and three situations are represented: rapid recovery, recovery in a few steps, and recovery in many steps. The changes in flow/volume, flow/time, and volume/time relationships are indicated. The converse of these changes will indicate the changes occurring in the transition from a normal state to one of depressed function.

In studying these recovery pathways it must be realized that the system depicted would take an infinite time to reach a new equilibrium. This, however, is a common problem in physiology, and usually it is found that as the equilibrium point is approached the system breaks into haphazard oscillation about that point (Wesson and associates³²).

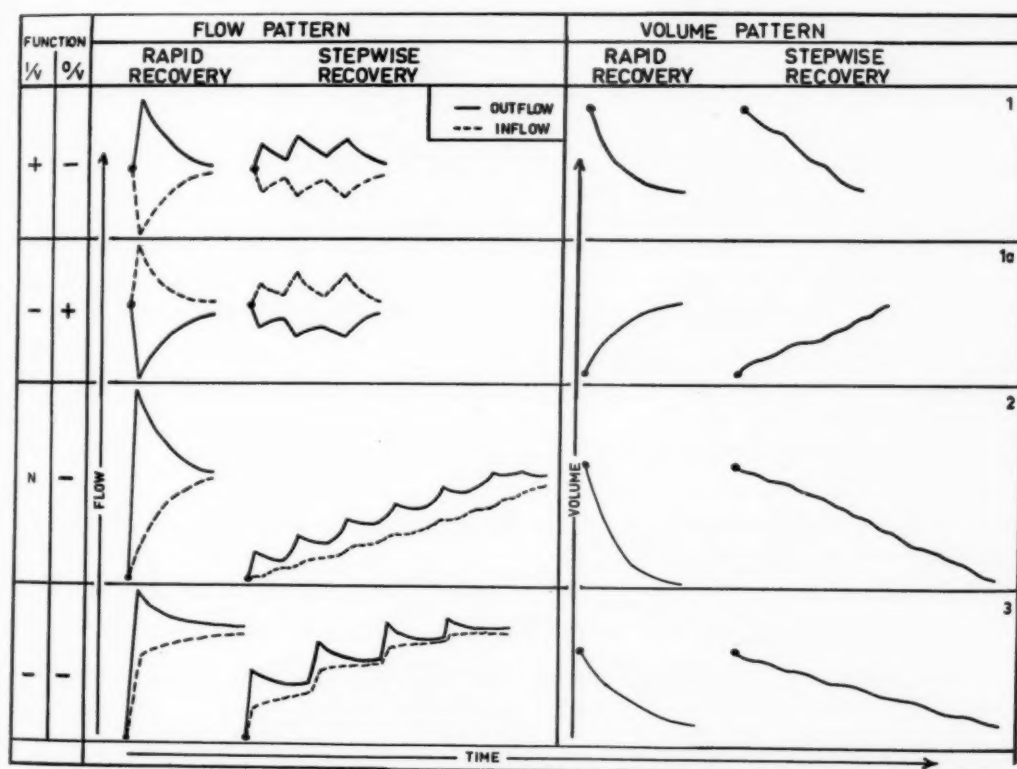


Fig. 5.—Diagram illustrating patterns of flow and volume related to time to be expected in two types of recovery from the abnormal equilibrium points 1, 1a, 2, and 3 shown in Fig. 3. Elevation, normality, or depression of the I/V or O/V functions are indicated, respectively, by +, N, and -.

The validity of this hypothesis was tested by comparing the changes predicted in given situations (Fig. 5) with those observed in patients. On the assumption that the relationships discussed are linear, the patterns of flow and volume change in recovery from a number of situations have been predicted and are shown to bear a striking resemblance to those seen in clinical conditions (Lowe²¹).

On this basis the behavior of the patient illustrated in Fig. 2 can be interpreted as follows. The first phase in which the volume increases, the outflow first falls and then rises, and the inflow falls, corresponds to rapid recovery

from a state of depressed inflow/volume and elevated outflow/volume function such as would be caused by a lowered osmotic pressure. It will be noted that this situation occurs at a point far displaced from the normal equilibrium volume.

The second phase, in which the outflow is raised above its initial value and the weight curve falls, corresponds to recovery in steps from a state of depressed outflow/volume function with a normal or perhaps depressed inflow/volume function. This interpretation is supported by the chart of outflow/volume function which reveals these steps (Fig. 2). No such clear-cut relationship between inflow and volume could, however, be demonstrated in this case.

The third section of the figure indicates that the system has returned to a substantially normal relationship and illustrates the oscillation of flow levels and volume about a normal equilibrium level.

In a system such as this the receptor mechanism is not preset to any level of volume, nor need it compare with any standard. So long as it is sensitive to change of the appropriate property and controls the inflow and outflow appropriately, the system will be self-regulating in respect to the property being maintained. The level at which the volume is maintained depends upon the characteristics of the inflow and the outflow mechanisms. If either of these changes the system will come to a new equilibrium at a different volume.

As the outflow mechanism contains the complex kidney as the outlet valve, the importance which physiologic studies have given to renal behavior in this connection is clear. It is also clear that a study of renal behavior alone cannot, as in fact it does not, explain all the phenomena seen in abnormalities of fluid volume regulation, because both inflow and outflow mechanism and the control mechanism must be considered. While little is known of the behavior of the inflow mechanism, the outflow mechanism consists of both a transport (circulation) and an excretory (renal) part.

APPLICATIONS OF THE HYPOTHESIS

The importance of this hypothesis based on "open" systems is that it draws attention to the need to consider both the solvent and solute when attempts are being made to correct disturbances of body fluid volume regulation. Also in such a complex system an abnormality at any one or more points in the mechanism can lead to a disturbance of body fluid volume regulation.

Thus, in the treatment of edema from congestive cardiac failure, both forced high intake of water (Schemm²⁷) and gross restriction of sodium intake have been advocated. To remove the edema fluid through the kidneys, both solvent and electrolytes must be excreted, but as there is an upper limit to the concentration of electrolytes in the urine, it is desirable for the urine volume to be as large as possible. To this end high fluid intakes have been advocated, but the outflow/volume function is independent of fluid intake level, and the increase in urine flow which follows a high intake is achieved at the expense of an increase in volume. Conversely, restriction of fluid intake would, by producing a fall in volume, reduce the volume of urine outflow and so the level of electrolyte

excretion. Alterations in the level of electrolyte intake might also disturb the concentration of electrolytes in the body fluids unless the outflow mechanism can correct this, and so, also, further disturb volume regulation. According to the hypothesis put forward, variation in the level of fluid intake may make some change in the volume of fluid stored, increased intake tending to increase and decreased intake to reduce its volume. Secondly increase of fluid intake, by increasing urine outflow, may permit correction of an abnormal osmotic pressure in the body by allowing greater excretion of electrolytes, and this correction in turn will perhaps permit a reduction of the edema fluid—it might of course increase it and, in fact, in some patients it does so.

It would seem desirable in such patients to provide a fluid intake adequate to enable correction of any osmotic abnormality and to reduce the electrolyte intake to a level below that being excreted, but, except in rare cases, extreme changes of either probably do not help greatly.

The prime necessity in treating these patients is to improve the outflow/volume relationship. Such improvement may occur spontaneously following rest in bed, following the exhibition of drugs improving the circulation, or following the exhibition of diuretic agents, such as mercurial diuretics.

Apart from giving a rationale to existing therapy for edema states, the concept provides a tool for research into their abnormal physiology. Thus this method has pointed out that in congestive cardiac failure there are in some cases several abnormalities which may disappear at different times. The outflow/volume relationship could provide a measure for the effectiveness of diuretic agents. This relationship is a measure of outflow function and, in fact, it is the basis of the Kepler-Power water excretion test used in the diagnosis of Addison's disease.

Further, the concept unifies a considerable number of factors which operate in the control of body volume, and it removes the anomaly (Starr,²⁸) that it was difficult to explain the importance of the heart in the physiology of edema formation in cardiac failure.

Finally, it seems likely that the concept of open systems should be as applicable in most metabolic studies as in the study of water metabolism.

SUMMARY

Conclusions based on observations of the changes in fluid intake and output and body weight made on 265 patients are reviewed. These patients were suffering from conditions in which there was a disturbance of body fluid volume regulation.

On the basis of these observations a hypothesis depending on the concept of "open" systems is developed and discussed. This hypothesis envisages the fluid storage of the body as a continuous flow system with a control mechanism sensitive to changes in both volume and osmotic pressure of some part of the stored fluid.

Some applications of this hypothesis are considered.

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THE HYPOCHOLESTEROLEMIC EFFECT OF PHENYLETHYLACETIC ACID AMIDE IN HYPERCHOLESTEROLEMIC ATHEROSCLEROTIC PATIENTS

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AN EXTENSIVE literature¹⁻⁵ appears to demonstrate that there is a relationship—possibly causal—between alterations of lipid metabolism and pathogenesis of human atherosclerosis. Attempts to lower the cholesterolemia would thus be justified, as a possible measure to prevent or reduce atherosclerotic changes.

A variety of means aimed at lowering the plasma cholesterol level have been suggested, but the results obtained with the various agents, including the ones proposed very recently,^{6,7} are rather controversial and disappointing.

Cottet and associates⁸ recently reported that phenylethylacetic acid, and more especially its amide, is effective in lowering the blood cholesterol level. This substance, studied as a choleric agent and obtained by breakdown of the molecule of dehydrocholic acid, was formerly believed to exert a hypocholesterolemic action either by increasing the biliary elimination of plasma cholesterol or by acting as a false metabolite in the endogenous synthesis of cholesterol from acetoacetic acid. Actually the mechanism of action of phenylethylacetic acid amide is still obscure. Apparently its effect is not due to stimulation of thyroid secretion, since the drug does not influence the basal metabolic rate.⁸ It is unable to prevent alimentary hypercholesterolemia and, thus, it does not act through interference with the intestinal absorption of cholesterol. The hypercholesterolemia induced by benzylthiouracil is not modified by the simultaneous administration of phenylethylacetic acid amide.⁸

Experimental results obtained in normally fed rats confirm the hypocholesterolemic effect of the drug.⁸ It has been demonstrated that the plasma cholesterol values, very constant as a rule in the rat, were 15 per cent lower at the end of six months of treatment with phenylethylacetic acid amide; this finding is statistically significant.

In experiments on human beings Cottet and associates⁸ obtained encouraging results in a mixed group of ninety-one persons. In 86 per cent of their cases the plasma cholesterol dropped to 50 per cent of its initial value.

Later Mathivat and Cottet⁹ extended the research and made a clinical study of phenylethylacetic acid amide in seventy-three persons, both normal and suffering from miscellaneous complaints. The group included fifty-five

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TABLE I. VARIATIONS OF CHOLESTEROLEMIA IN THE 14 PATIENTS DURING PHENYLETHYLACETIC ACID AMIDE TREATMENT AND ONE MONTH AFTER DISCONTINUING THE DRUG

NO.	NAME	AGE (YRS.)	SEX	INI- TIAL CHOLE- STEROL EMIA	WEEKS OF TREATMENT										ONE MONTH AFTER END OF TREAT- MENT							
					FIRST		SECOND		THIRD		FOURTH		FIFTH				SIXTH		EIGHTH		TENTH	
					A	B	A	B	A	B	A	B	A	B			A	B	A	B	A	B
1	G.A.	62	F	378	0	209	-44.7	204	-46	131	-65.3	250	-33.8	215	-43.1	154	-59.2	110	-70.9	270	-28.6	
2	D.L.	57	M	280	-23.2	232	-17	215	-23.2	193	-31	264	-5.7	232	-17	135	-31	135	-51.8	238	-15	
3	P.D.	50	M	223	+6.7	183	-17.9	140	-37.2	154	-30.9	264	+18	140	-37.2	140	-37.2	163	-26.9	278	+24.6	
4	S.A.	56	M	226		163	-27.9	145	-35.4	163	-27.9	202	-10.6	168	-25.7	183	-19	100	-55.7	178	-21.2	
5	C.A.	43	M	220	-2.3	200	-9	188	-14.5	163	-25.9	257	+16.8	264	+20	178	-19	158	-28	193	-12.2	
6	F.G.	46	M	239	-7.9	226	-5.4	193	-19.2	193	-19.2	365	+52.7	183	-23.4	168	-29.3	178	-25.5	215	-10	
7	N.P.	57	M	272	-38.2	204	-25.7	164	-39.7	168	-38.2	168	-38.2	163	-40	184	-32.3	145	-46.3	220	-19.1	
8	N.U.	61	M	204		226	+10.8			183	-10.3			182	-10.8	193	-5					
9	G.F.	66	M	232	-26.3			155	-33.2	131	-43.5	215	-7.3	145	-37.5	145	-37.5			215	-7.3	
10	F.L.	64	M	220	+5	178	-19	124	-43.6	188	-14.5	128	-41.8	154	-30	154	-30			292	+32.7	
11	P.E.	70	M	226	-11.5	232	+2.6	140	-38	145	-35.8											
12	L.M.	47	M	245	-46	215	-12.2	178	-27.3	178	-27.3											
13	R.M.	50	M	378	-38.6	215	-43.4	178	-52.9	354	-6.3											
14	F.G.	41	M	264	-9.8	154	-41.6	238	-9.8													

A = Plasma cholesterol (milligrams per 100 c.c.).

B = Percentage change from the initial level.

TABLE II. MEAN VALUES AND PER CENT REDUCTION OF PLASMA CHOLESTEROL FOR THE 10 PATIENTS TREATED FROM EIGHT TO TEN WEEKS

	INITIAL VALUE	WEEKS OF TREATMENT								ONE MONTH AFTER END OF TREAT- MENT
		FIRST	SECOND	THIRD	FOURTH	FIFTH	SIXTH	EIGHTH	TENTH	
Mean value (mg. per 100 c.c.)	249.4	229.6	202.2	169.7	166.7	234.7	184.6	169.2	141.2	233.3
Mean per cent reduction		8.2	18.8	32.1	33.3	6	27	32.1	43.3	6.8

patients with arteriosclerosis. The initial plasma cholesterol level ranged from normal to 400 mg. per 100 c.c. and in sixty-three subjects was above 200 mg. per 100 c.c. The dosage used was 2 to 3 Gm. daily. It was found that in a high percentage of cases (92 per cent) the plasma cholesterol was significantly lower (the reduction varied from a minimum of 7 per cent to a maximum of 50 per cent of the initial values) at the end of two to twelve weeks of treatment; in thirty of the patients the lowering of plasma cholesterol ranged from 21 per cent to 50 per cent of the initial level. The incidence and degree of the hypocholesterolemic effect was in direct proportion with the initial cholesterolemia. It was noted that at times the effect was prompt (first week of treatment), at other times less prompt (two to three weeks), and at still other times it was delayed (four to seven weeks). No toxic or undesirable side effects were noted, except for mild and transient gastric symptoms occurring in 7 to 8 per cent of the patients. The chemical constituents of the blood and the renal function did not show any changes attributable to the drug.

Extending the studies of the French authors we have investigated the effect of phenylethylacetic acid amide on the plasma cholesterol level of a group of hypercholesterolemic and presumably atherosclerotic patients.

MATERIAL AND METHOD

Among the patients attending our out-patient department and among the private patients of one of us we selected fourteen subjects, ranging in age from 39 to 70 years, who were presumed to be atherosclerotic on the basis of clinical, electrocardiographic, or roentgenologic evidence, and in whom the plasma cholesterol content was above 200 mg. per 100 c.c.

During the months preceding our study the cholesterolemia of the patients had shown a certain variability; at no time, however, the plasma cholesterol content had been less than 200 mg. per 100 c.c. As is shown in Table I, at the onset of treatment the plasma cholesterol ranged from 204 to 378 mg. per 100 c.c. The mean cholesterol value for the ten patients treated over a period of eight to ten weeks was 249.4 mg. per cent; for the patients treated for three to four weeks the mean value was 278.2 mg. per cent.

The plasma cholesterol was determined according to Bloor's method. The determinations were repeated at weekly intervals throughout the period of treatment and at the end of one month after treatment was discontinued.

All of our patients had been on a low-fat diet for months or years prior to our study; the dietary regimen was continued throughout our investigation. We do not know, however, whether all of them adhered strictly to the prescribed diet, which contained approximately 500 to 600 mg. of cholesterol and 20 to 30 Gm. of neutral fat per day. Although some of the hypercholesterolemic patients exhibited a tendency toward lower cholesterol values on the low-fat diet, none of them attained normal cholesterol levels.

Phenylethylacetic acid amide was given in 0.50 Gm. tablets after meals, in the daily dose of 2 Gm. during the first two weeks and of 3 Gm. thereafter. Treatment was continued for periods ranging from four to ten weeks, the mean period being eight weeks.

All the other therapeutic measures were suspended, except those that were considered necessary on account of the special cardiocirculatory condition of the patient (cardiotonics, aminophylline, trinitrin). Otherwise the patients were allowed to pursue their normal activities without any restrictions beyond those dictated by their cardiocirculatory condition.*

RESULTS

Throughout the period of observation there were no complaints attributable to the drug. The clinical picture did not show any significant change; two patients stated that their attacks of anginal pain were less frequent and less severe, but in all likelihood this was due either to spontaneous variations or to autosuggestion.

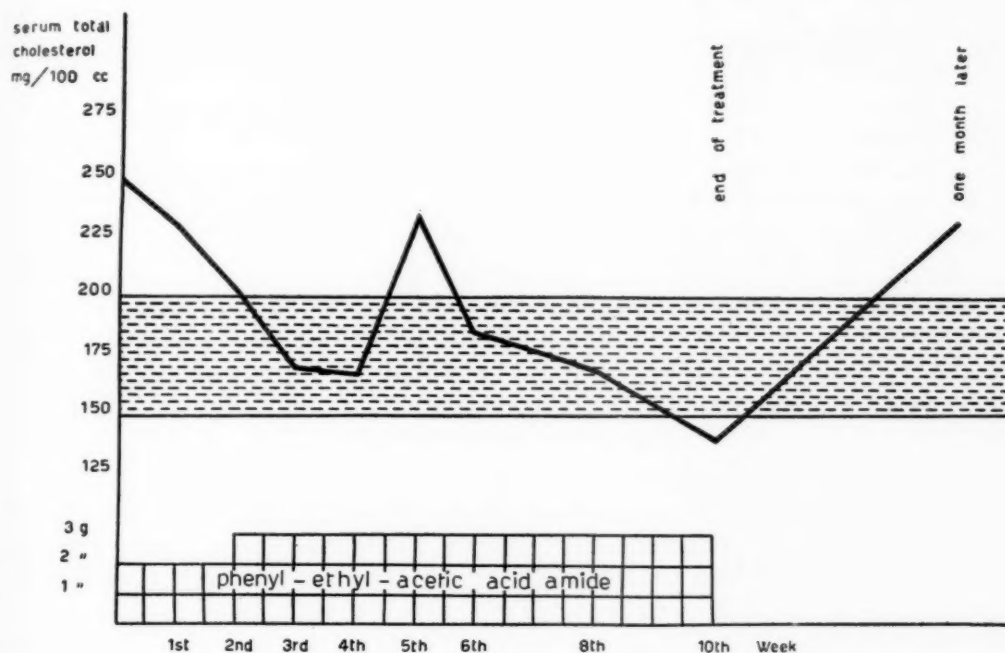


Fig. 1.—Mean values for plasma cholesterol in the ten patients treated for eight to ten weeks at varying intervals during treatment with phenylethylacetic acid amide and one month after withdrawal of the drug. The shaded area corresponds to normal values.

The individual data of the variations of cholesterolemia are shown in Table I. It will be noted that in at least some of the measurements made during the period of treatment all the patients except one (Case No. 8) showed a reduction of plasma cholesterol amounting to well over 10 per cent of the initial value.

*One additional patient was studied. This was a 39-year-old man (B.S.) who had suffered a myocardial infarction in the past. His pretreatment plasma cholesterol value was 168 mg. per 100 c.c. After eight weeks of treatment in the daily dose of 2 to 3 Gm., the cholesterolemia dropped to 124 mg. per 100 c.c. This patient is not included in the present series because, owing to his low initial cholesterol value, he is not homogeneous with the general group.

The per cent reduction in individual patients treated for eight to ten weeks ranged from 71 to 5 per cent. The mean per cent reduction for this group as a whole was 43.3 per cent at the time of the last observation before discontinuing the drug (Table II).

As a general rule the hypocholesterolemic effect appeared during the first week of treatment; it became much more pronounced during the third week, when the daily dose was raised from 2 to 3 Gm.; during the fifth week the effect was less evident, and it finally attained its maximum during the tenth week, at the end of the period of treatment.

As shown in Fig. 1, the mean plasma cholesterol content dropped to normal (150 to 200 mg. per 100 c.c.) for the major part of the period of treatment and even fell below normal during the tenth week.

One month after discontinuing the drug the plasma value was only 6.8 per cent below the initial mean and this difference, in contrast with the differences observed during treatment, is not statistically significant.

DISCUSSION

The present results are in reasonable agreement with those reported by Mathivat and Cottet. They reported a maximum lowering of 50 per cent in the plasma cholesterol; our greatest effect was a reduction of 71 per cent in one patient but this patient had a very high initial value (378 mg. per 100 c.c.). We found a return to near the pretreatment values a month after discontinuing the drug, the mean per cent reduction being 6.8 per cent. Mathivat and Cottet, instead, reported that at the end of two to twelve weeks after the drug was withdrawn the plasma cholesterol level in about half of their subjects had not risen much above the lowest values attained during treatment, and had returned to the pretreatment level in the remaining 50 per cent.

The discrepancy between our results and those of Mathivat and Cottet is probably due to differences in the conditions of the experiment. Among their patients there were eighteen subjects without any evidence of atherosclerosis and ten with a normal initial cholesterol value. Moreover, the mean duration of treatment was shorter for their patients than for ours. Finally, the French authors do not mention whether their patients were, like ours, on a dietary regimen with a very low fat content. The foregoing differences may account for the discrepancy in results.

It is worthy of note that the plasma cholesterol dropped well below the normal level in two of our patients (Nos. 1 and 4—to 110 and 100 mg. per 100 c.c., respectively), and slightly below the normal level in four additional patients. It is likely that such a marked effect was due to the combined effect of the drug and the drastic dietary fat restrictions. None of the patients studied by Mathivat and Cottet showed lowering of plasma cholesterol below the normal level.

At the present state of our understanding of the role of cholesterol in the pathogenesis of atherosclerosis, we do not feel that it would be justified to conclude that a drug having a hypocholesterolemic effect, such as phenylethylacetic acid amide, may provide the answer to the therapeutic problem of atherosclerosis.

The alteration of cholesterol metabolism possibly associated with atherosclerosis may be qualitative rather than quantitative. We do not know whether a purely quantitative reduction of plasma cholesterol can correct the metabolic disorder responsible for the development of atherosclerosis.

As regards phenylethylacetic acid amide, we believe that further research concerning the metabolism of cholesterol and long-term extensive experimental investigations, both on men undergoing atherosclerotic changes and on animals with experimental atherosclerosis, are needed in order to assess the value of a sustained lowering of the cholesterolemia for the management and prevention of atherosclerosis.

SUMMARY

A group of fourteen atherosclerotic patients with pronounced hypercholesterolemia were treated with phenylethylacetic acid amide, in the daily dose of 2 Gm. during the first two weeks and of 3 Gm. thereafter, for periods ranging from three to ten weeks (mean eight weeks). A significant reduction (well over 10 per cent) of plasma cholesterol occurred in all of the patients except one. The per cent reduction ranged from 71 to 5 per cent. Among the ten patients who received the drug for eight to ten weeks, the mean reduction at the end of treatment was 43.3 per cent. The mean plasma cholesterol value dropped to normal for the major part of the period of treatment, and even below normal during the tenth week. One month after discontinuing the drug the cholesterolemia had again risen to near the initial value.

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STUDIES ON THE ANTICOAGULANT PHENINDIONE

III. ITS USE IN AMBULATORY PATIENTS

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SINCE reports first appeared on the use of long-term anticoagulation for the prophylaxis of intravascular clotting¹⁻⁴ there has been a growing interest in this type of program. During 1954 alone, reports were made describing over 2,000 patients on such programs⁵⁻⁸ for the prevention of myocardial infarction, thrombophlebitis, pulmonary embolus, peripheral emboli, and other miscellaneous conditions involving intravascular coagulation. The results have been promising. For example, in coronary artery disease Suzman⁸ reported a gross mortality rate of 7.3 per cent in a treated group contrasted to 33 per cent in an untreated group. Nichol,⁶ in reporting a cooperative study, found mortality rates of 12.3 per cent and 29 per cent in treated and control groups, respectively. Owren⁵ experienced a mortality rate of 5 per cent in a treated group followed an average of about one and one-half years. If these trends are corroborated, long-term anticoagulation is the first distinct preventive agent in arteriosclerotic disease. In prevention of emboli from fibrillating hearts, success has been varied. Whereas eight of Cosgriff's⁹ twenty-eight patients had emboli during treatment, Tulloch and Wright¹⁰ reported twenty-eight probable episodes in thirty-eight cases under treatment. Others^{11,12} report almost complete suppression of emboli. Although the evidence indicates that successful suppression of emboli can be achieved in most instances, some cases probably will develop an occasional embolus even under what is considered to be adequate therapeutic control.

Three major drawbacks to long-term anticoagulation have been repeatedly emphasized: (1) variability of response to the anticoagulant requiring frequent prothrombin determinations; (2) hemorrhage; and (3) persistent thromboembolism alluded to above.

The variability of response appears to be related to the prolonged and cumulative effect of dicoumarol which has been the most commonly employed preparation. Thus Marple and Wright,¹³ and Cosgriff,⁹ as well as others, recommended that the interval between prothrombin determinations be no longer than one

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week, or at the most two, except in special circumstances. The former authors comment that the dose of dicoumarol needs to be "juggled in a manner analogous to the determination of the exact insulin requirements of a difficult and labile case of diabetes mellitus." Owren and Aas¹⁴ feel that by use of the "P and P" method of determination of the combined level of prothrombin and proconvertin, and by making very fine adjustments of the daily dosage of dicoumarol, more accurate control can be achieved. Nevertheless they recommend intervals between prothrombin determinations of no more than three weeks when the levels are stable although "in some patients with a very stable P and P level the interval may be further increased to 4 or 5 weeks but as a rule it is not recommended." Even though the dose of dicoumarol be adjusted to a very accurate degree, most patients require dosage adjustment from time to time because of the marked cumulative effect.

The incidence of hemorrhagic manifestations has been reported to vary from about 4 per cent⁵ to 25 per cent.⁶ Minor hemorrhages such as epistaxis, ecchymoses, and minor hematurias are very frequent and are usually excluded in the tally. Serious hemorrhages are infrequent and fatal hemorrhages occur in less than 1 per cent of cases. The latter have been exclusively cerebral and the relation to anticoagulants is not entirely clear. Intraperitoneal, retroperitoneal, intraarticular, gastrointestinal, and vaginal hemorrhages have been reported.

The use of phenindione (P.I.D.) in place of dicoumarol for long-term anticoagulation has been mentioned briefly by several authors. Dedichen,¹⁵ however, used phenindione exclusively in fifty-five patients. He claimed a remarkable degree of uniformity of effect from a single standard dose schedule on an out-patient basis, and thirty-seven of his fifty-five patients required no dose change after two months. Owren⁵ mentioned the use of phenindione compared with dicoumarol and felt it was "superior to dicoumarol particularly for long-term anticoagulant treatment. The variation in individual sensitivity to P.I.D. is less pronounced than to dicoumarol and therefore it is usually easier to obtain the optimal level of hypocoagulability. Unpredictable changes in the P and P level . . . are less apt to occur with P.I.D." This he felt might be explained on a difference in absorption. He also considered hemorrhagic complications were less frequent. Kruesi and Schilling¹² used phenindione in nine ambulatory patients but did not find a uniform response. This report is made for the purpose of outlining the details in regard to use of phenindione in a long-term anticoagulant program.

METHODS AND MATERIALS

Prothrombin times were done by the one-stage method of Quick using commercial dried rabbit brain thromboplastin (Difco) and calcium chloride 0.01 molar. All patients received phenindione* in doses adjusted so that their prothrombin time was between 26 and 36 seconds. This range represents "prothrombin activity" of between 5 per cent and 10 per cent of normal on the basis

*Kindly supplied as Danilone by Charles E. Frosst, Ltd. of Canada and by Schieffelin & Co. of New York.

of curves made from pooled normal plasma diluted with fresh BaSO₄-adsorbed (25 mg. per milliliter) human plasma. These percentage figures should not be confused with those derived from curves made from dilutions with saline.¹⁶ The limits were set arbitrarily at the onset of the study, but as a result of an investigation of the effect of phenindione on the coagulation mechanism and the finding of plasma thromboplastin component deficiency developing late in the course of phenindione administration,^{17,18} the limits of prothrombin times were reduced to twenty to thirty seconds during the last six months of study. Thirty-three individuals were given phenindione on an ambulatory out-patient basis for the prevention of various conditions involving spontaneous intravascular coagulation. All patients were first examined for signs or symptoms of bleed-

TABLE I. DISTRIBUTION OF CASES ACCORDING TO DIAGNOSIS

DIAGNOSIS	NUMBER OF CASES
Rheumatic heart disease, auricular fibrillation, and peripheral emboli	16
Arteriosclerotic heart disease, auricular fibrillation, and peripheral emboli	2
Unknown heart disease, auricular fibrillation, and peripheral emboli	1
Thrombophlebitis, recurrent pulmonary emboli with cor pulmonale	2
Thrombophlebitis, pulmonary embolus without cor pulmonale	6
Peripheral vascular disease	4
Recurrent myocardial infarction	2

ing tendencies and had control laboratory studies consisting of bleeding time, clotting time, and tourniquet test. All but two were started on phenindione while in-patients and were observed usually for two weeks before discharge. Although a cumulative effect of phenindione is clearly present in some patients,¹⁹ hospitalization is not necessary if small doses are given initially with gradually increasing increments until the desired prothrombin times are achieved. After discharge, patients were followed twice a week at first. Later we found the intervals could safely be reduced to once a week and finally once a month. Later, all patients have been followed once a month. Meticulous juggling of dosage to offset changes in prothrombin times has not been necessary. If the dosage is altered as little as possible, differences in prothrombin times from week to week can be seen to be merely natural or laboratory fluctuations. In most cases, after three months the dose could be kept constant from month to month and even year to year.

Phenindione was given twice a day, preferably every twelve hours, in accordance with the suggestion of Jaques,²⁰ because in short-term use a twelve-hour dose schedule resulted in more uniform response and a smaller dose.¹⁹ If bleeding occurs, phenindione may be stopped before the full daily dose has been given.

TABLE II. DISTRIBUTION OF CASES ACCORDING TO AGE AND SEX

AGE GROUP (YEARS)	NUMBER OF CASES	
	MALE	FEMALE
Under 30	0	1
31-40	2	5
41-50	7	6
51-60	4	2
Over 60	4	2

RESULTS

From patient to patient, the average daily dose of phenindione required to maintain prothrombin time within therapeutic limits varied widely as it is known to do with dicoumarol and Tromexan. The smallest daily dose was 25 mg. and the greatest 300 mg. No correlation could be established with sex, age, or weight. In a given individual, however, the dose from time to time varied in a manner outlined in Table III. During the first three months about half of the patients needed less drug to maintain the prothrombin time at desired levels. The dose had to be reduced an average of 29 per cent (range 15 to 57 per cent) in sixteen of the thirty-three patients. No change in dose was necessary in nine patients, and eight patients required an average increase in dose of 29 per cent. The largest decrease in dose was noted in a man (Case 18) who developed increasing congestive heart failure, while the largest increase (300 per cent) was noted in a man (Case 22) who was emerging from extreme congestive heart failure. Although congestive failure was present in nine others, large changes in dose requirement were not experienced. Case 20 was originally resistant but eventually required smaller doses.

After three months the dose remained stable enough so that the latest dose remained the same as it was at three months in ten of the twenty-three who had been followed for twenty-three weeks or more. In only three did the dose have to be increased, and this increase averaged only 12 per cent. Again nine patients needed less drug to maintain the prothrombin time within the limits, and the average decrease in dose was 25 per cent.

In general, therefore, most patients develop a gradual increase in sensitivity to phenindione which is more apparent during the first three months, but continues in some even after that. A relatively small decrease in the dose is necessary to correct these changes. Although some correction of dose up and down may be necessary from time to time, in our experience the results are most satisfactory if this is kept to a minimum and the changes in dose are kept around 20 to 25 per cent.

In several patients a single daily dose was compared with a split daily dose, and no significant variation was noted. This is in contradistinction to short-term therapy where a more uniform effect and smaller dose was achieved with the daily dose divided into two equal parts with a twelve-hour interval.¹⁹

TABLE III

CASE	DIAGNOSIS	DURATION OF TREATMENT (WEEKS)	AVERAGE DOSE AT 1 MONTH (MG./DAY)	AVERAGE DOSE AT 3 MONTHS (MG./DAY)	CHANGE IN DOSE FIRST 3 MONTHS (%)	AVERAGE DOSE MOST RECENT (MG./DAY)	CHANGE IN DOSE AFTER 3 MONTHS (%)
1	RHD, E	7	200	200	0		
2	T, PE	8	50	41	-18		
3	T, PE, ASD	8	200	100	-50		
4	PVD	8	100	100	0		
5	RHD, E	8	200	200	0		
6	RHD, E	9	100	75	-25		
7	T, PE	10	200	200	-0		
8	RHD, E	11	75	50	-33		
9	RHD, E	15	50	75	+50	75	0
10	T, PE, RHD	17	100	75	-25	75	0
11	T, PE, CP	18	50	50	0	50	0
12	Cor	23	200	125	-37	125	0
13	T, PE	24	300	200	-33	200	0
14	T, PE, E, CP, ASD	25	100	114	+14	114	0
15	RHD, E	27	75	100	+33	100	0
16	Cor	27	200	150	-25	175	+13
17	RHD, E	36	50	50	0	50	0
18	Cor, E	52	150	65	-57	65	0
19	PVD	57	200	125	-37	125	0
20	PVD	58	300	200	-33	125	-38
21	RHD, E	66	46.2	50	+7	35	-30
22	RHD, E	90	25	100	+300	75	-25
23	RHD, E	94	200	150	-25	113	-25
24	Cor, E	118	100	87	-13	93	+6
25	T, PE, Cor	124	150	175	+17	225	+29
26	RHD, E	144	57	57	0	50	-12
27	U, E	156	100	100	0	100	0
28	RHD, E	158	100	125	+25	100	-20
29	RHD, E	168	50	75	+50	50	-33
30	RHD, E	179	50	50	0	50	0
31	RHD, E, T, PE	192	100	75	-25	63	-16
32	PVD	196	38	38	0	25	-33
33	RHD, E	215	200	150	-25	150	0

Abbreviations: ASD = atrial septal defect; Cor = coronary artery disease; CP = cor pulmonale; E = peripheral embolus; PE = pulmonary embolus; PVD = peripheral vascular disease; RHD = rheumatic heart disease; T = thrombophlebitis; and U = heart disease unknown etiology.

Prothrombin Time.—The adequacy of treatment and danger of overdosage was analyzed by a study of the prothrombin times. Of a total of 1150 prothrombin-time determinations while on treatment, fifty-four (4.7 per cent) were below twenty seconds.* Therefore on most occasions (95.3 per cent) when a prothrombin time was taken the patient was within a theoretically protective zone. Overdose as judged by prothrombin times of over forty seconds occurred sixty-seven times or 5.8 per cent. Little risk was apparent from overdosage per se since there were only two episodes of bleeding, which amounted to minor hematuria, during these periods. All other bleeding occurred with prothrombin times in the therapeutic range. The highest prothrombin time was sixty-four seconds and only eleven (1 per cent) were over fifty seconds. Omission of drug

*These figures are exclusive of Case 32 whose prothrombin time was kept between eighteen and twenty-five seconds for reasons described later in the text.

for one day was sufficient to allow the prothrombin time to return to the proper level. Slightly over half of the occasions when the prothrombin time was over forty seconds represented sudden jumps when the patient had been on a steady dose for several weeks or months, while the others reflected overcorrection for a previous drop in prothrombin time.

Bleeding.—Almost all patients exhibited a bleeding tendency in one way or another. This usually took the form of minor ecchymoses, hemoptysis, epistaxis, microscopic hematuria, occasional blood streaking of stools, and a tendency for cuts to bleed longer than usual. Those instances where the drug was either continued or where one or two doses were omitted, as was frequently done by the patients on their own accord, have been excluded as significant bleeding episodes. Where Vitamin K₁ was used, the patient was admitted to the hospital because of bleeding, or the drug stopped for over three days, the episode has been counted as a significant bleeding episode. Hematuria was experienced in four cases, and no lesion was seen by intravenous pyelogram in any. All four were started on the drug again without recurrence of hematuria.

TABLE IV. SIGNIFICANT BLEEDING EPISODES EXPERIENCED IN NINE CASES*

Hematuria	4
Melena	3
Epistaxis	2
Hemoptysis	1
Laceration	1
Menorrhagia	1
Generalized Bleeding	1
Total	13

*Case 32 had three episodes and Cases 27 and 33 two each.

On the contrary, two of the three who had melena showed lesions of the gastrointestinal tract by x-ray, an ulcer, and diverticulitis, respectively. Two were stopped and the third had reached the end of the treatment period. Epistaxis was severe in one patient and required use of Vitamin K₁ Emulsion intravenously. Although hemoptysis occurred in seven patients with pulmonary congestion, in six its occurrence was not out of proportion to what had been experienced by them prior to anticoagulation. In one patient with mitral stenosis, however, an episode of hemoptysis was severe. Of the seven women regularly menstruating, only one of menopausal age experienced menorrhagia. She was continued on treatment without further problems after uterine curettage.

The most troublesome bleeder (Case 32) was a man, aged 64, with peripheral vascular disease and diabetes, who had hematuria. Phenindione was stopped for three weeks but was again started when arterial insufficiency of a toe recurred. Again, bleeding occurred in the form of epistaxis and ecchymoses, and as a compromise this patient's dose was reduced so that the prothrombin time was kept between eighteen and twenty-five seconds. After thirty-eight months

on treatment he developed a generalized bleeding episode with severe epistaxis, hematuria, melena, and purpura. The prothrombin time was only 20.9 seconds, two-stage prothrombin 8 per cent, proconvertin 6 per cent, labile factor over 150 per cent, bleeding time infinite, clotting time forty-four minutes, and the tourniquet test negative. Platelet count and clot retraction were normal. Further study showed a deficiency of plasma thromboplastin component induced by phenindione. Details of this will be reported elsewhere.¹⁸ Vitamin K₁ Emulsion given intravenously was followed by complete cessation of bleeding in three hours. Two months later he had a mild cerebral vascular accident and he was again given phenindione. He has continued for eight months without further bleeding.

Reasons for Termination of Treatment.—The general plan has been to keep on permanent anticoagulant therapy those patients with: (1) peripheral emboli from fibrillating hearts, (2) arteriosclerotic problems, and (3) recurrent pulmonary emboli resulting in pulmonary hypertension and chronic cor pulmonale. A limited period of treatment of two to six months has been arbitrarily designated for those with pulmonary emboli from phlebitis but without pulmonary hypertension and chronic cor pulmonale. Patients with mitral stenosis who underwent valvulotomy and auricular appendectomy were felt to be sufficiently protected to terminate treatment.

TABLE V. REASONS FOR TERMINATION OF TREATMENT

Treatment period ended	6
Valvulotomy and auricular appendectomy	3
Died congestive failure	2
Stopped of own accord	2
Bleeding	2

In fifteen patients treatment was terminated for the reasons outlined in Table V. In six patients with pulmonary embolus without chronic cor pulmonale, the period of treatment was ended and phenindione was stopped. In three patients valvulotomy and auricular appendectomy were performed. Two patients died of congestive failure. Two stopped treatment on their own accord, and two were stopped because of bleeding.

Interruptions in Treatment.—In ten patients, the course of treatment was interrupted temporarily because of minor operative procedures, bleeding, and experimental use of Vitamin K₁. These interruptions totalled fourteen patient months.

Thromboembolic Episodes.—The thirty-three patients have been on treatment for a total of 542 patient months. During this time two episodes have occurred which could have been thromboembolic. One individual with mitral stenosis, auricular fibrillation, and renal and pulmonary emboli before treatment developed pleuritic pain, hemoptysis, and density by x-ray at the right lung base. A second with mitral stenosis, auricular fibrillation, and renal and cerebral emboli before treatment developed renal colic without urinary changes or ab-

normality by intravenous pyelograms. These two episodes were considered pulmonary and renal embolus, respectively, and both occurred when the prothrombin time was within the therapeutic limits set.

In four of the ten patients whose treatment was interrupted for a total of 14 patient months there were 5 thromboembolic episodes. These occurred after ten days, two weeks, three weeks, seven weeks, and two months of stopping treatment. In the four who stopped treatment because of bleeding or who defaulted, follow-up is available only in two who are well at one and two years, respectively. Therefore there has been a total of 5 episodes in 50 patient months' observation of patients not on anticoagulants. One death occurred in the eight whose treatment period was ended purposely. This was probably a recurrent pulmonary embolus, fourteen months after stopping treatment.

Toxicity.—NPN, PSP, and BSP tests in fourteen patients showed no evidence of renal or hepatic toxicity.

DISCUSSION

There is very little factual material for comparison of phenindione with dicoumarol. It is our impression, however, that in the case of phenindione the dose variation from one individual to another is large and much the same as with dicoumarol. In regard to constancy of dose within the same individual, moreover, it is possible that the two drugs are similar. With a given dose of dicoumarol, however, the prothrombin time tends to rise or fall gradually over many weeks, at which time the dose has to be altered.¹⁴ Except for the general slight downward trend in dose, this was not so of phenindione. After three months the dose remained constant in almost half of the patients. Further, we believe that there are less sudden unpredictable rises and falls in prothrombin time with phenindione than with dicoumarol. Whereas we were easily able to keep the prothrombin time within limits of twenty to forty seconds 90 per cent of the time, Tulloch and Wright succeeded only 78 per cent of the time with dicoumarol, and 59 per cent with Tromexan.

Severe bleeding was experienced in about the proportion one would expect with dicoumarol. Hematuria seemed to be particularly prevalent, and oddly enough has not recurred after reinstating treatment in any case. Hematuria appears to be a temporary complication, and phenindione probably can be started again safely after a seven- to ten-day pause. Gastrointestinal bleeding is an indication of underlying disease and warrants further study. Some degree of ecchymosis and epistaxis occurs in nearly all patients but is usually not troublesome. Menstruation in women is not affected by phenindione and is not a contraindication to its use. Because of the danger of recurrent thromboembolism, interruption of treatment for long periods of time should be avoided in those who are considered to need anticoagulation permanently. In those whose treatment was interrupted, three episodes of thromboembolism which occurred within two weeks could have been consistent with an "overshoot effect," namely, a return of the coagulation mechanism to a hypercoagulable state. This finding supports the concept of "tapering off" the anticoagulant rather than stopping abruptly. Two other episodes, however, seemed too late to be con-

sidered as an overshoot effect. At present we feel treatment should be permanently stopped: (a) only if the treatment period is ended and (b) if on repeated attempts bleeding recurs.

SUMMARY

Phenindione was used as an anticoagulant in thirty-three patients on a long-term basis. The prothrombin time was kept between twenty-six and thirty-six seconds originally, and twenty to thirty seconds during the latter part of the study. The dose of phenindione required usually decreased during the first three months. Thereafter it remained constant in 50 per cent of the cases and required little change in the others. Little trouble was had in keeping the prothrombin time within the prescribed limits if the dosage changes were kept small. Significant bleeding occurred in 27 per cent of cases, but nearly all patients noted minor evidences of a bleeding tendency. Thromboembolic episodes during treatment occurred twice in two patients during 565 patient months; whereas it occurred five times in four patients during 50 patient months when treatment was interrupted or stopped before it should have been. No toxicity other than bleeding was experienced. Phenindione is considered to be somewhat superior to dicoumarol in long-term anticoagulation as a result of a steadier effect on the prothrombin time.

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A BIOLOGIC TEST FOR DIGITALIS EFFECT

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DETERMINATION of the optimal dose of a digitalis preparation for any given patient still remains a constant challenge in the management of the failing heart. Although the various digitalis glycosides possess similar pharmacodynamic actions, they differ in therapeutic characteristics: rates of absorption and elimination; degree of cumulation; duration of latent period, and margin of safety. Although each manufacturer attempts to guide clinicians in the proper "digitalizing" doses of their own preparations, the suggested dosages usually are based on rather gross clinical signs supported by the knowledge that higher doses will usually be accompanied by clinical and ECG evidence of digitalis toxicity. Actually, objective evidence of the minimal dose required to produce a desired clinical effect has not been demonstrated.

It is generally believed that digitalis has no effect on the normal heart. In 1951, Walton and Gazes¹ presented evidence that digitalis does increase the contractile force of the normal dog heart. Later, Darby and his associates,² working in the same laboratory, showed that experimentally elevated blood pressure in the dog resulted in decreased cardiac contractile force and a poor acceleration BCG. If, despite the maintenance of this elevated blood pressure, the heart force was augmented, the abnormal BCG reverted to normal (Diagram A).

These findings were applied in our BCG study of hypertensive human subjects.³ It was shown that the abnormal BCG frequently found in severely hypertensive patients (Fig. 2,A) could be reverted toward normal (Fig. 1) by either decreasing the heart load (lowering the blood pressure) or increasing the heart force (digitalizing) (Fig. 2,B). Either procedure restored the balance of cardiovascular forces.

The present study was undertaken to extend these observations on digitalis effect. Our limited objectives were: (1) to determine the dose of cardiac glycoside required to improve the ballistocardiograms of hypertensive patients; (2) to determine the dosage beyond this that caused the BCG again to deteriorate.

Two preparations, digitoxin and gitalin (Gitaligin†) were compared in this initial phase of the study.

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†Gitaligin supplied by White Laboratories, Inc., Kenilworth, N. J.

SELECTION OF CASES

The patients were selected from the Hypertensive Clinic of the Jersey City Medical Center without reference to age, degree of arteriosclerosis, or duration of hypertension. Patients were rejected from this study if they had normal or borderline ballistocardiograms, if they had now or had ever had symptoms or signs of congestive heart failure, or if they had ever taken digitalis.

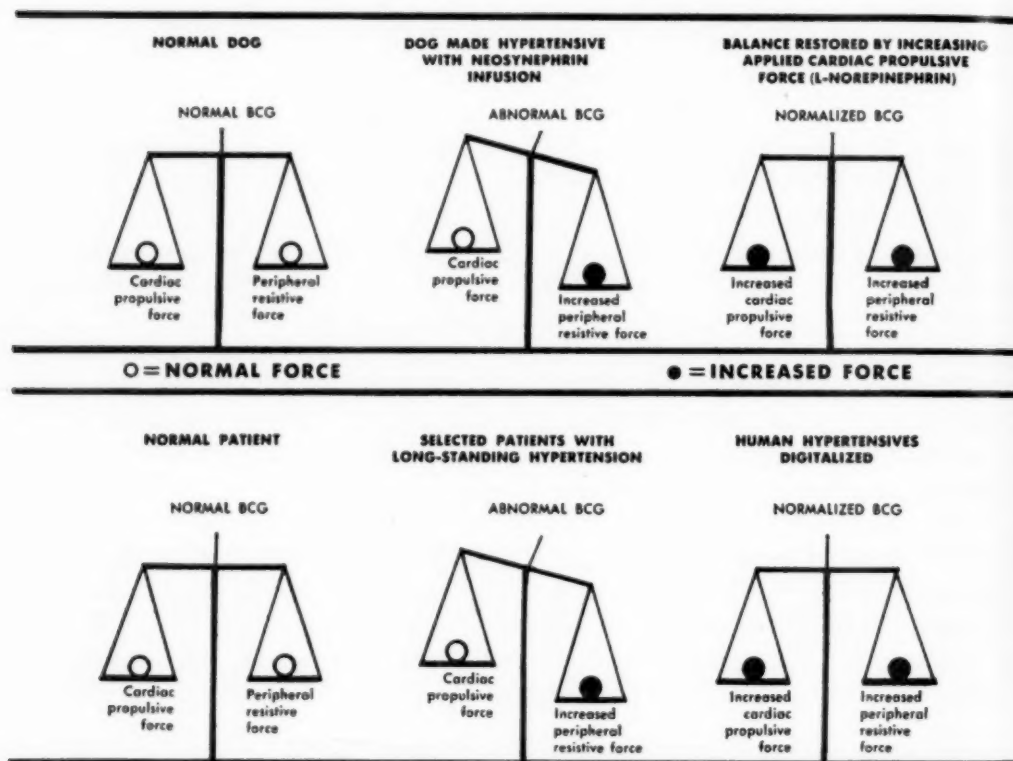


Diagram A.

Those remaining as test subjects had tracings corresponding to Grade III and IV in the Brown classification.⁴ They ranged in age from 37 to 53 years and had a history of high blood pressure of 2 to 20 years' duration. None had ever had symptoms or signs of congestive heart failure. Approximately 60 per cent had normal-sized cardiac shadows on x-ray examination; the remaining 40 per cent were slightly enlarged. The ECG's were normal in approximately 35 per cent and showed patterns of left ventricular hypertrophy or strain in the remaining 65 per cent.

Most of the patients received digitoxin and gitalin in alternate courses during the study, with a digitalis-free interval of at least three weeks between courses.

None of the patients had received hypotensive drugs during the month prior to digitalization. During this preliminary observation period all were placed on placebos. Their blood pressures were found to be relatively stable on repeated checks and ranged from 150/100 mm. Hg to 230/150 mm. Hg. Frequent

examinations showed a constant degree of abnormality in the BCG's of all the subjects. Displacement, velocity, and acceleration tracings were taken with the D.V.A. ballistocardiograph.⁵

PROCEDURE

Digitoxin.—The test procedure involved the taking of a BCG tracing on all subjects the day preceding initial administration of digitoxin and one tracing every day thereafter for the duration of the experiment.

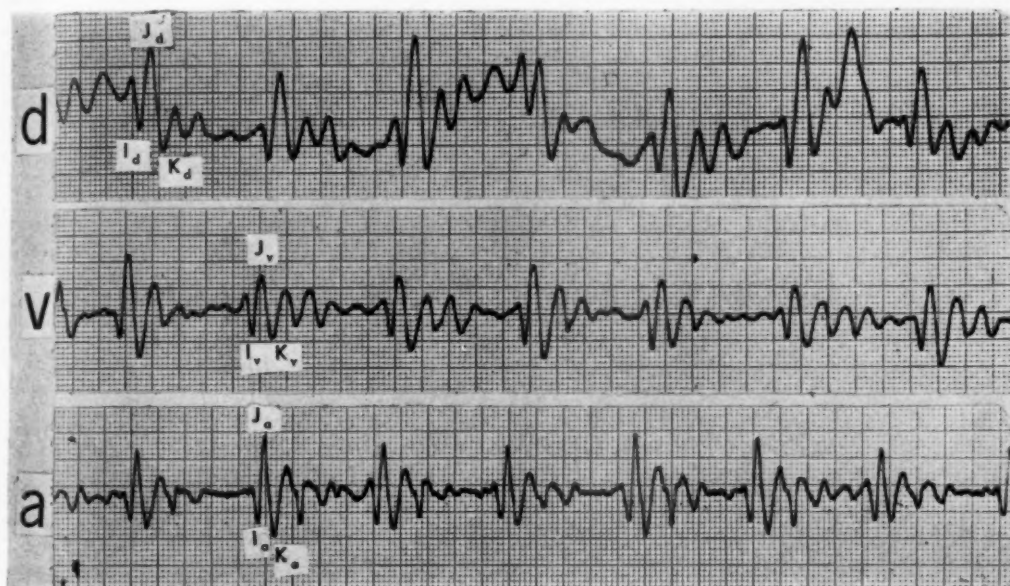


Fig. 1.—Normal direct-body ballistocardiogram recorded in displacement, velocity, and acceleration.

On the first treatment day, fifteen subjects, eight men and seven women, received 0.6 to 0.8 mg. of digitoxin. On the second day, additional doses were given to make a total of 1.2 mg. for each patient. On the third day, two patients received 0.2 mg., or a total of 1.4 mg. each, and two other patients received 0.4 mg. or a total of 1.6 mg. each, in the same period.

Gitalin.—The procedure used in the testing of gitalin was similar to that employed for digitoxin. An exception should be noted in that the doses of gitalin were slightly in excess of comparable recommended clinical therapeutic doses of digitoxin. Repeated BCG's were taken at intervals similar to those described for digitoxin.

Eleven test subjects, six men and five women, were given 4.0 to 5.5 mg. of gitalin on the first test day. On the second day, they received additional doses which brought the total amount of gitalin in forty-eight hours to 7.0 to 8.0 mg. Additional doses of from 2.0 to 3.0 mg. in ten subjects on the third day brought the total dose in these patients to 9.0 to 11.0 mg. in seventy-two hours.

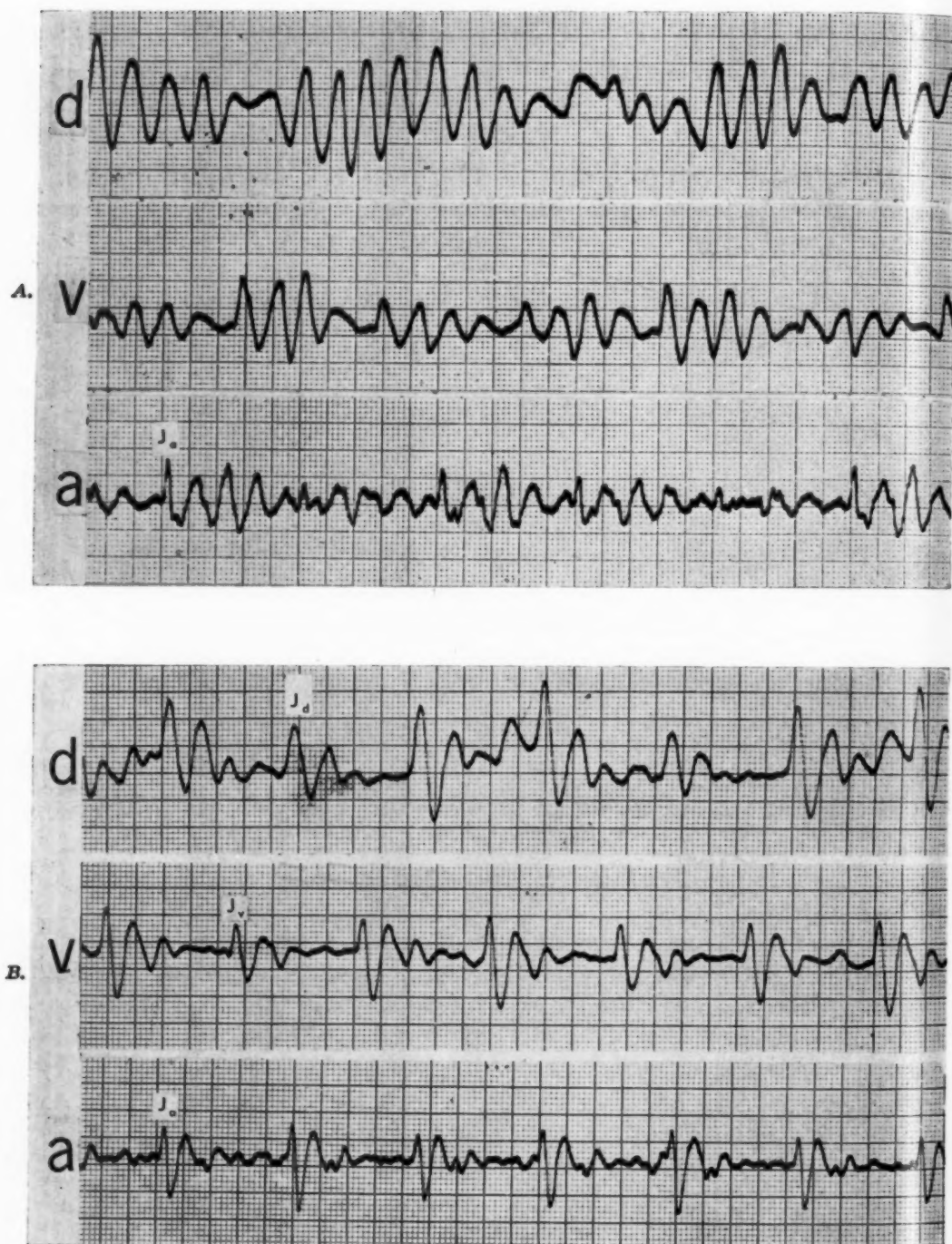


Fig. 2.—*A*, Abnormal BCG of a severely hypertensive patient. No other evidence of disturbed myocardial function is present. *B*, BCG taken from the same patient twenty-four hours after he had received 5 mg. of gitalin. The complexes are repetitive and the tracing conforms with the definition of a normal BCG. The form of the individual complex is, however, abnormal in that the *I* force is almost absent. This is one of the best "digitalized" BCG's, lesser degrees of improvement being the rule.

RESULTS

The results of the administration of digitoxin to fifteen patients and of gitalin to eleven similar patients, as measured by changes in their BCG's (all of which had been classified as abnormal prior to treatment), are shown in Tables I and II.

Digitoxin.—Six subjects with initially chaotic BCG's were given 0.6 to 0.8 mg. of digitoxin during the first twenty-four hour test period. All BCG tracings returned to normal, or near normal. On the second test day, the addition of 0.4 to 0.6 mg. of digitoxin resulted in the deterioration of the BCG in four of the patients. An additional dose of 0.4 mg. of digitoxin on the third day completed the downgrading of the entire group (Fig. 2,C).

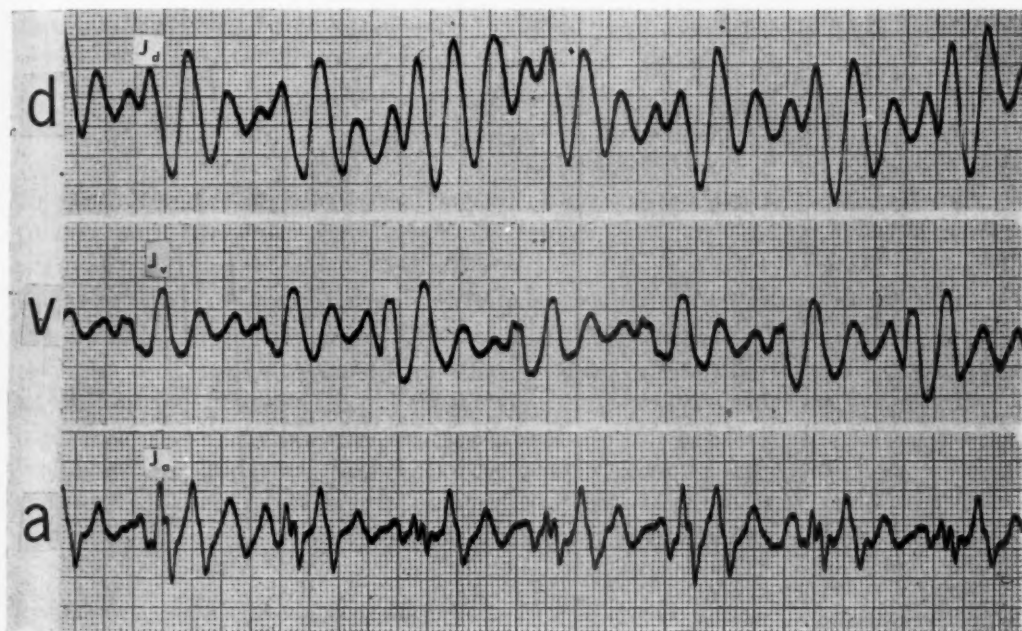


Fig. 2.C.—BCG deterioration as evidence for excessive dosage of gitalin (11 mg. in seventy-two hours). At this time, in this patient, neither clinical nor ECG signs of overdigitalization are as yet present.

Nine of the test patients who had had moderately abnormal BCG's initially were given 0.6 to 0.8 mg. of digitoxin during the first twenty-four-hour test period. Eight of the nine responded with improved BCG's, one showed deterioration. The eight subjects were then given additional 0.4 or 0.6 mg. doses on the second day and they continued to improve. Two of the eight who improved were given additional doses of 0.2 mg. on the third day. BCG's of both of these patients thereafter showed deterioration.

The one subject whose initial moderately abnormal BCG showed deterioration following 0.6 mg. of digitoxin on the first test day later became chaotic after the total dose of 1.2 mg. on the second day. Subsequently, this subject received a total dose of 9.5 mg. of gitalin over a period of three days without deterioration of his BCG.

TABLE I. DIGITOXIN

BCG	CHAOTIC			MODERATELY ABNORMAL		
Time	24 hrs.	48 hrs.	72 hrs.	24 hrs.	48 hrs.	72 hrs.
Number of patients	6	6	2	9	8	2
Total dose of digitoxin	0.6-0.8 mg.	1.2 mg.	1.6 mg.	0.6-0.8 mg.	1.2 mg.	1.4 mg.
Result	All improved	2 improved 4 deteriorated*	2 deteriorated	8 improved 1 deteriorated	8 improved	2 deteriorated

*Observations discontinued when BCG deteriorated.

Gitalin.—On the first test day six subjects with chaotic BCG's were given from 4.0 to 5.5 mg. of gitalin. All subsequent BCG's showed improvement. They were then given additional doses to a total of from 7.0 to 8.0 mg. on the second day, and again showed normal or quasinormal BCG's. On the third day, four received a total of 10 mg. and two a total of 11 mg. All six showed deterioration of their BCG's following these last doses.

Five patients with moderately abnormal BCG's were given 4.0 to 5.5 mg. of gitalin on the first test day. Four improved and one deteriorated. Additional doses to total 7.0 to 8.0 mg. on the second day in the four that improved produced continued BCG improvement. They all deteriorated, however, on the third day following total doses of from 9.0 to 10 mg.

TABLE II. GITALIGIN

BCG	CHAOTIC			MODERATELY ABNORMAL		
Time	24 hrs.	48 hrs.	72 hrs.	24 hrs.	48 hrs.	72 hrs.
Number of patients	6	6	4 2	5	4	4
Total dose of gitaligin	4.0-5.5 mg.	7.0-8.0 mg.	10.0 mg. 11.0 mg.	4.0-5.5 mg.	7.0-8.0 mg.	9.0-10.0 mg.
Result	All improved	All improved	All deteriorated	4 improved 1 deteriorated*	All improved	All deteriorated

*Observations discontinued when BCG deteriorated.

The individual whose BCG had become worse with the initial doses of gitalin continued to deteriorate and became chaotic with additional doses on the second test day. No explanation can be suggested for this atypical response.

SUMMARY

It has long been known that the abnormal BCG in human cardiac decompensation will revert toward normal as the heart contractile force is augmented by digitalization. It has not been accepted that digitalis can, in a like manner, augment the cardiac contractile force in patients who show no clinical symptoms or signs of decompensation. Nevertheless, in the cases presented here this seems to be the most likely explanation for the reversion of the abnormal tracings to normal. The increased peripheral load caused by arterial hypertension in these patients resulted in abnormal BCG's. Despite the fact that the hypertensive load remained the same, the traces were normalized by digitalis. The balance between propulsive force and resistive force was restored, albeit at a higher level.

Applied to the quantitative study of digitalis, it may safely be assumed that the dose required to normalize a given BCG is near the optimal digitalizing dose for that particular patient at that particular time. No further assumptions can be made. But even this limited information has two important applications. In the first place, if the patient's cardiac status and blood pressure load remains unchanged, the method should be useful in comparing the therapeutic range of various cardiac glycosides. Secondly, in a given decompensated patient, it seems that the method might be helpful in determining the quantity of digitalis required for maximum therapeutic effect. Parenthetically, in a preliminary investigation of this application it was immediately apparent that the minimal dose was higher and the therapeutic range was narrower than those reported in this study.

Further studies are in progress using smaller increments of digitalis to titrate more accurately the therapeutic ranges of several digitalis preparations. Another study will attempt to correlate the clinical, electrocardiographic, and ballistocardiographic signs of restored compensation in patients with congestive heart failure.

CONCLUSION

1. This is a preliminary report presenting a method for measuring digitalis effect by means of the ballistocardiograph.
2. The abnormal BCG found in many hypertensive patients can be reverted to or toward normal by an adequate dose of digitalis. The smallest amount of the drug required to produce this change can be looked upon as the minimum therapeutically active dose. Larger quantities of the preparation cause the BCG again to deteriorate.
3. The amount of cardiac glycoside required to produce the desired BCG effect in these patients is consistently less than the "digitalizing" dose for decompensated patients.

4. The comparative data on the effects of two glycosides, gitalin and digitoxin, are presented to show that a measurable difference exists between them. No conclusions as to the superiority of either drug can be drawn from this study.

5. It is felt that further studies with this method are warranted in both compensated and decompensated patients.

SYNOPSIS

Patients with long-standing hypertension often have abnormal ballistocardiograms. Although they are not caused by decompensation, these abnormal traces can be converted to normal, or near normal, by an adequate dose of digitalis. It is felt that this is a measure of the direct effect of digitalis on the heart muscle and that the normalized BCG is evidence for the restored balance between the propulsive forces and the resistive forces in the cardiovascular system.

The method is proposed as a biologic test for the determination of the minimal therapeutic dose of digitalis.

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Clinical Report

ELECTROCARDIOGRAPHIC FINDINGS OF PERICARDITIS AND HISTOPLASMIN SENSITIVITY

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RECENTLY calcification of the pericardium in the presence of histoplasmosis, as seen by x-ray, has been reported in two cases.¹ The report pointed up the possibility of histoplasmosis as another causative agent of pericarditis. It seems reasonable that histoplasmosis, like tuberculosis, can cause pericarditis with or without calcifications. This report is of a case with electrocardiographic changes of pericarditis, pulmonary calcifications, a strongly positive histoplasmosis skin test, negative tuberculous and coccidioidomycosis skin tests, and recurrent uveitis. This is the first case report of the electrocardiographic findings of pericarditis in the presence of histoplasmosis.

CASE REPORT

The patient, a 38-year-old man, was seen in consultation in September, 1955, for evaluation of recurrent gastrointestinal symptoms, uveitis, and an abnormal electrocardiogram. The majority of his complaints began in 1952 while living in Abilene, Tex. He had intermittent diarrhea, borborygmus, and cardiospasm. Upper and lower gastrointestinal series were normal. He stated that he was a somewhat tense individual and that when under pressure he had more severe gastrointestinal symptoms. In September, 1952, and in November, 1953, he was a member of an expedition to Peru. Immediately prior to departure in November, 1953, he developed a severe sore throat. This persisted for three or four weeks of the expedition. The roof of his mouth, cheeks, and throat were sore. He described ulcerations like "canker sores" in the mouth. The cervical lymph glands were tender. The finger tips were sore. A postnasal drip was present and he suffered from the previously described gastrointestinal symptoms. Following his return from the expedition, Dec. 23, 1953, a medical study was performed.

Laboratory examinations were as follows: white blood cells, 8,200 with 58 per cent neutrophils, 38 per cent lymphocytes, 1 per cent monocytes, and 1 per cent eosinophils; red blood cells, 4,800,000; hemoglobin, 15.9 Gm.; sedimentation rate, 4 mm. in one hour; hematocrit, 52 per cent; nonprotein nitrogen, 22 mg. per cent; creatinine, 0.6 mg. per cent; urinalysis, normal with specific gravity of 1.013; repeated stool examinations, negative for ova and parasites and

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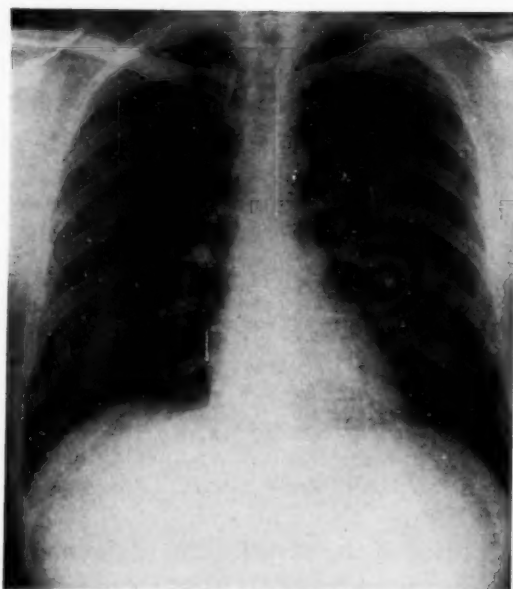


Fig. 1.—Chest x-ray demonstrating pulmonary calcifications of histoplasmosis of patient.

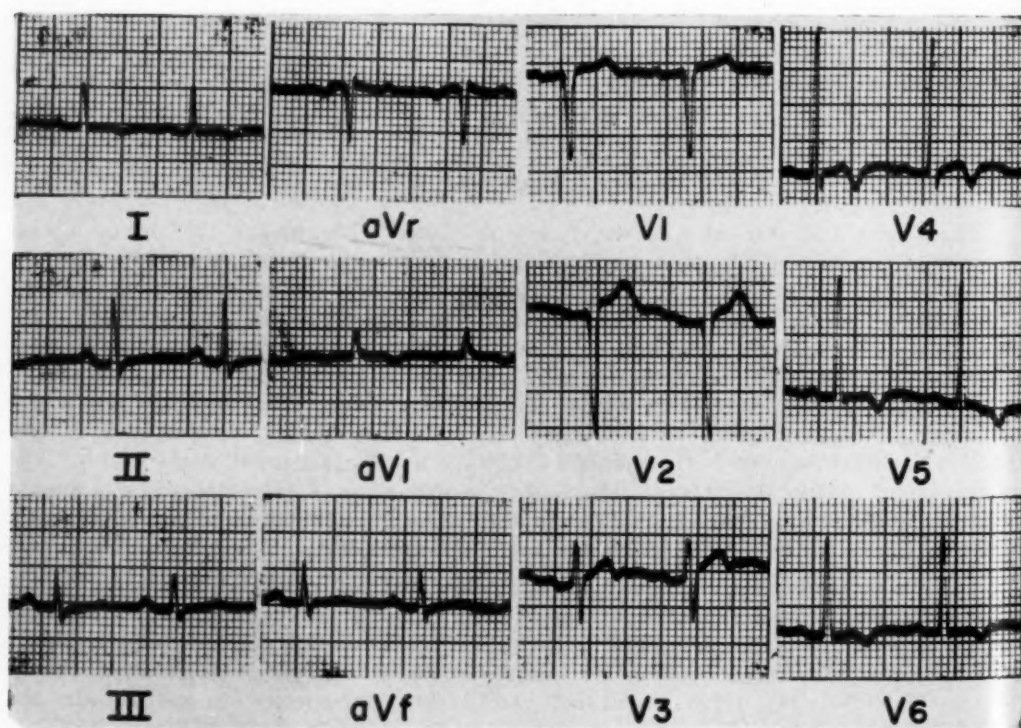


Fig. 2.—Electrocardiogram demonstrating T-wave changes of pericarditis.
Record recorded at full standard.

occult blood; Kahn, negative; typhoid, negative; Proteus O \times 19, negative. *Salmonella paratyphi A*, negative, *Salmonella paratyphi B*, negative; *Pasteurella tularensis*, negative; *Brucella abortus*, negative. Throat culture, normal flora.

Radiographic study of the gastrointestinal tract and gall bladder revealed no abnormalities. Chest x-ray and cardiac fluoroscopy were normal. (A review of the chest x-ray demonstrated calcifications, to be discussed later.)

An electrocardiogram was recorded which is closely similar to that of Fig. 2. There was inversion of T₁, T_{V4}, V₅, V₆. An exercise tolerance test was performed without any significant changes. The patient was always athletic and continued to perform strenuous sports and exercise following these studies with no ill effects. He continued to have intermittent gastrointestinal symptoms.

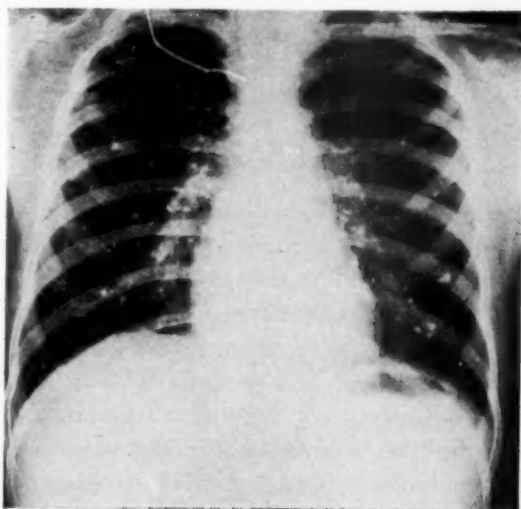


Fig. 3.—Chest x-ray of 12-year-old son of patient demonstrating wide-spread calcifications of histoplasmosis.

On Sept. 23, 1955, he developed swelling under the right eye associated with itching and burning. He noted a blind spot in his vision and consulted an ophthalmologist. Uveitis was noted on examination. The patient had a previous blind spot adjacent to the fovea in August, 1951, with a residual small scar. Visual disturbance persisted for three to four weeks, with gradual return to normal. Mild cellulitis of the infraorbital area continues to occur intermittently, subsiding with change in geographic locality. Medical evaluation, October, 1955, revealed no apparent abnormalities on physical examination other than the eye findings mentioned above. The blood pressure was 132/74 mm. Hg and cardiac examination revealed no abnormalities.

Laboratory studies, including complete blood count, hemoglobin, sedimentation rate, and urinalysis were within normal limits. Other studies included: blood uric acid, 8.5 mg. per cent; total protein, 6.93 mg. per cent; albumin, 5.55 mg. per cent; globulin, 1.43 mg. per cent; anti-streptolysin titer, 166 units; routine febrile agglutinations, *Brucella*, *Pasteurella tularensis*, and heterophil antibody, within normal limits; Sabin-Feldman dye test for toxoplasma, negative; and complement fixation test for histoplasmosis, blastomycosis, and coccidioidomycosis, negative. Chest x-ray demonstrated hilar calcifications (Fig. 1). Review of previous films demonstrated similar findings without significant change. Calcifications over the cardiac shadow could not be definitely localized to the pericardium by multiple views on fluoroscopy. Electrocardiogram (Fig. 2) demonstrated normal sinus rhythm, rate 90 per minute; P-R interval, 0.18 sec.; QRS duration, 0.08 sec.; Q-T interval, 0.34 sec.; Q-U interval, 0.48 sec.; P waves, normal; QRS complexes, normal; S-T segments, elevation of RS-T junction in V₁, V₂, and V₃; T waves, inverted in I, aV_L, V₄, V₅, and V₆; mean QRS axis +45 degrees; posterior with transition at V₃; T axis

+150 degrees, anterior with transition at V_3 ; spatial QRS-T angle, 119 degrees. Frequent tracings between December, 1953, and the above record demonstrated only minor changes in the amplitude of the T waves.

Skin tests for histoplasmosis, tuberculosis, and coccidioidomycosis were performed. The skin test was markedly positive for histoplasmosis and negative for tuberculosis and coccidioidomycosis.

It should be emphasized that since the onset of symptoms in 1952, the patient continued to perform more than average exertion, including distance running, football, baseball, and treadmill exercises without evidence of cardiac embarrassment or pain.

Significant epidemiologic data include residence in Tennessee to adult life. His wife is from Kansas and in recent years they established a home in Abilene, and San Antonio, Tex.

A 12-year-old son fractured his collar bone in January, 1954. Calcifications were noted in the lung fields and are unchanged (Fig. 3). Recent skin tests were strongly positive for histoplasmosis and negative for tuberculosis and coccidioidomycosis. Hilar calcifications were noted in the wife and 10-year-old and 5-year-old daughters, but skin test for tuberculosis, histoplasmosis, and coccidioidomycosis were negative in all three.

DISCUSSION

It is tempting to explain the entire course of events in this case on the basis of histoplasmosis. The lesions of the mouth and throat with cervical adenopathy could well have been secondary to histoplasmosis or, on the other hand, unrelated to the other findings. Gastrointestinal symptoms are common in histoplasmosis. Chorioretinitis and uveitis is also a manifestation of histoplasmosis. One might advocate the possibility of pericarditis secondary to other infections; however, no other infection was definitely established. Certainly if one may presume pericarditis to be secondary to tuberculosis in the presence of a positive tuberculin test, the corollary should be equally valid for histoplasmosis. Histoplasmosis is suggested as another cause for pericarditis and its electrocardiographic findings.

SUMMARY

A case history of a patient with pulmonary calcifications, positive skin test for histoplasmosis, and negative skin test for tuberculosis, uveitis, and electrocardiographic evidence of pericarditis, is presented. Histoplasmosis is considered as a possible causative agent for pericarditis and its electrocardiographic findings.

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Review

THE NEPHROTIC SYNDROME

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NEPHROSIS or the nephrotic syndrome in its pure form is a noninflammatory kidney disease which usually produces massive albuminuria and edema, low serum proteins, and increased blood lipids. It is associated with normotension and with normal kidney function by clinical methods. Mixed forms are common in which hypertension is present and in which renal function is compromised to varying degrees.

The term nephrosis in this discussion will refer to patients presenting the above clinical picture regardless of whether microscopically the kidney glomeruli show membranous lesions or those of subacute glomerulonephritis.

PATHOLOGIC ANATOMY

Grossly.—The kidneys are enlarged, smooth, pale, and the capsule strips with ease. The cut surface is greasy, and red and yellow streaks are apparent.

Microscopically.—The glomeruli may appear normal in autopsy material. However, thickening of the glomerular membrane may frequently be demonstrated with special stains,¹ though a significant number of nephrotic kidneys fail to show changes even with these special stains.^{2,3} Electron microscopy,⁴ however, has demonstrated striking distortion and smudging of the podocytes or epithelial cells of the glomerular basement membrane in patients who showed no changes under light microscopy, even with special stains. An unusual feature is reported in fresh renal biopsy material by Kark and Pirani⁵ in that the glomeruli show marked congestion of the capillaries in nephrosis, whereas they are relatively bloodless in normal kidneys. The congestion disappears after successful treatment with steroids. In addition to the above findings, those of subacute glomerulonephritis, namely, epithelial crescents and adhesions of the glomerular tuft to Bowman's capsule, may also be present. The basement membrane may encroach upon the capillary lumen in either disease and produce hyalinization of the glomerulus from ischemia.

ETIOLOGY, DIFFERENTIAL DIAGNOSIS, AND INCIDENCE

Ever since Bell⁶ revealed the relationship between acute, subacute, and chronic glomerulonephritis, a stormy controversy has raged about the identity of lipoid or chronic nephrosis with the nephrotic syndrome of glomerulonephritis. Fishberg¹³ sums up the evidence very well. Bell,⁶ Moschovitz,⁷ Allen,⁸ and Elwyn⁹ all feel that the diseases are identical because of (1) the rarity of purely degenerative lesions, (2) the progression of cases from acute glomerulonephritis to nephrotic phases, and (3) the typical nephrotic patients who show glomerulonephritis at autopsy (and more recently with needle biopsy). (Barnett and associates,¹⁰ Heyman and Alperin,¹¹ and Metcoff and collaborators¹² agree.) On the other hand Fishberg,¹³ Kantrowitz and Klemperer,² and Murphy¹⁴ have seen examples of nephrosis in which no thickening of the glomerular membrane can be demonstrated even with connective tissue stains. Furthermore, the development of the end-stage kidney with hypertension and renal failure, Fishberg feels, does not preclude the diagnosis of pure nephrosis since encroachment upon the capillaries by thickened basement membrane may produce hypertension and glomerular hyalinization with renal failure.

Some recent evidence favoring the unitarian, or one disease concept has been presented by Vernier and collaborators⁴ in four siblings, each of whom had various types of nephrosis by autopsy or open biopsy. One died of renal insufficiency and was found to have chronic glomerulonephritis. A second had transient "pure nephrosis." The third had chronic nephrotic syndrome and his biopsy revealed subacute glomerulonephritis. A fourth had had "pure nephrosis" from birth and biopsy showed normal kidney. All four had classical smudging and distortion of the podocytes, or glomerular basement membrane cells, by electron microscopy. The incidence of both types of disease in the same family and the finding of identical lesions in the glomerulus in all cases by electron microscopy strongly favor the concept, though do not prove that the diseases are the same.

The fact that the drugs trimethadione¹⁵ and paramethadione¹⁶ can produce a typical nephrotic picture shows that all cases are not necessarily of inflammatory origin. Gold, calomel, and bismuth¹⁰ can produce it, and cases have been reported to be associated with constrictive pericarditis¹⁷ which are relieved by surgery. Several cases of thrombosis of the renal veins in adults are described with the clinical picture of nephrosis,¹⁷⁻²⁰ and one showed renal lipodosis at autopsy. (Renal vein thrombosis in children presents an entirely different picture.) In addition, renal amyloidosis may produce a nephrotic picture and, in one series of eight adult nephrotic patients in which needle biopsy was employed, four had amyloid disease.²¹ Supposedly, primary amyloidosis involves the kidneys in only 25 per cent of the cases, while secondary reveals kidney involvement in about 70 per cent.²² Recent biopsy material suggests that a higher percentage of the cases are primary in nature than was once thought. Amyloid disease is usually associated with a high blood gamma globulin while nephrosis has a low one.

Diabetic nephropathy has a nephrotic picture of a sort, but when full-blown it usually also is associated with hypertension and renal failure. Lupus, in our

needle biopsy material, is one of the more common causes of a nephrotic picture. In addition to needle biopsy, we perform a biopsy of any sort of rash appearing in patients with renal disease, no matter how nondescript, and are not infrequently surprised to have the pathologist return a diagnosis of lupus. Periarteritis in rare instances can produce the syndrome. All patients with the nephrotic syndrome should be carefully questioned about skin eruptions and joint pains and, if present, should cause one to suspect the possibility of a collagen disease.

Cases complicating various types of bacterial infections are probably examples of latent cases exacerbated by those infections. Pneumococcus is a frequent complicating infectious agent. Cases reported with tuberculosis²³ are probably either amyloid or chance occurrences. Syphilis, however, is firmly established as an occasional cause of the disease.

One further disease can mimic nephrosis, namely, myxedema. Considerable proteinuria in our experience may be associated with severe myxedema, especially if heart failure results, and the high blood cholesterol and clinical appearance may also be misleading. This does not occur often,²⁴ but has confused us on two occasions. The blood serum proteins should help differentiate these conditions. Both may have soft edema if heart failure is superimposed upon the myxedema.

Anaphylactoid purpura with renal involvement might be confused with a mixed type of nephrosis associated with hematuria since ecchymotic lesions are not rare in nephrotic children, and since nephrotic edema has been described in patients with anaphylactoid purpura.²⁵

Incidence.—Cooke,²⁶ Rothenberg,²⁷ and Riley²⁸ estimate variously from 0.4 to 0.6 new cases per year per 100,000 population, or 1.8 per 1,000 live births by age 5 years, or 7.25 cases per 100,000 total population under 5 years of age.²⁶ Males predominate about two to one. Several examples of familial occurrence have been cited^{4,29} and the instance reported above of three cases in one family is noteworthy. The author has been informed of an example in two brothers, but these examples are rare. Eighty per cent of the cases occur under the age of 5 years. One case is reported as present at birth.³⁰

PATHOGENESIS

Proteinuria.—Proteinuria is not uncommonly the only symptom of the disease and may be the only residual symptom between exacerbations of the edema. Ninety per cent of the protein is albumin. The proteinuria could be produced by either increased glomerular filtration or decreased tubular reabsorption. The lesions in the tubules were so striking that the latter concept found much favor at first. Tubular reabsorption of protein is now widely accepted, as cited by Squire,³¹ because proteins stained with hemoglobin, Evans blue dye, or labelled with fluorescent material are found in the mitochondria of the proximal tubular cells. Brewer³² actually saw hemoglobin in the canals of the brush border of the tubular cells extending from the lumen into the cells. Sellers and collaborators³³ calculated that as much as one-third of the circulating protein is filtered and passes through the tubular cells each day. More hemoglobin and less globulin than albumin are reabsorbed.³⁷ Govaerts³⁴ showed an

actual threshold for tubular reabsorption of protein. Hardwicke³⁵ studied simultaneous clearances of albumin, globulin, and creatinine following albumin infusions. As the serum albumin level rose, globulin reabsorption by the tubules was apparently blocked by the increased albumin, and more globulin appeared in the urine despite the fact that the serum globulin level was not altered. Squire³⁶ worked out actual albumin filtration and clearance figures and Spector³⁷ learned that in experimental acute nephritis there is probably increased reabsorption by the tubules. Clearance studies indicate that increased filtration rather than decreased tubular reabsorption is the important feature of nephrosis.

In nephrosis, increased glomerular permeability to acacia,³⁸ egg albumin, and Congo red dye³⁹ have been found. About the same relative proportions of albumin and globulin appear in the urine with less of the larger molecule globulin, but little or no fibrinogen is found despite the high serum level in nephrosis.^{40,41}

Epstein⁴² thought that since egg albumin is eliminated there might be an abnormal protein formed in nephrosis, but plasma transfusions from nephrotic to normal subjects failed to cause albuminuria in the recipient.

Hypoproteinemia.—Hypoproteinemia could be a result of (1) decreased synthesis, (2) increased destruction, or (3) simple loss in the urine.

The vast majority of patients will lose less than 10 to 20 Gm. of albumin a day. Co Tui⁴³ has proved that normal subjects can synthesize 50 Gm. of protein a day, yet in nephrosis the serum albumin falls. This has led to investigation of the other two facets of this problem. In contradistinction to the idea of decreased synthesis, Drabkin and Marsh find that synthesis is actually increased and there is also no sign of increased destruction.⁴⁴ Why the body is unable to replace the relatively small losses of albumin in many cases has been a mystery. In answer to this, Fishberg¹³ found that high protein feeding over a long period of time can raise the serum albumin if proteinuria is not greater than 5 Gm. a day. Blahd and associates⁴⁵ found albumin synthesis to be increased in three out of four adult nephrotic patients, and that the rate was directly related to dietary intake. The reason that protein synthesis of nephrotic victims does not keep up with urinary loss is most likely because they have insufficient protein intake.

Lipemia.—Lipemia is striking and produces a milky serum. Fishberg⁴⁶ removed blood from dogs and reinfused the cells until the serum proteins fell to a low level, at which time the blood lipids rose. Others⁴⁷ have not been able to repeat these results, but recently Rosenman, Byers, and Friedman⁴⁸ have established the relationship between hypoproteinemia and lipemia beyond a doubt. In rats with antikidney-serum nephrosis, they showed that prevention of protein loss by ureteral ligation or ureteral-vena caval anastomosis prevented development of lipemia. Artificial maintenance of normal plasma albumin levels by continuous intravenous infusion of plasma albumin both prevented the rise in lipids and cholesterol in the animals and reduced both to normal when they were already present. As the infused albumin disappeared from the circulation, the lipemia gradually returned. Artificial reduction of the albumin with plasmapheresis augmented the lipemia. The cause of the phenomenon is under active investigation and may be related to the transport role of the serum proteins in lipid metabolism.

EDEMA

Since Starling's classical experiments⁴⁹ the importance of serum proteins and their osmotic effect in the reabsorption of fluid from the interstitial spaces has been known. Leiter⁵⁰ produced edema in animals by plasmapheresis, namely, removal of blood and reinfusion of cells. The mechanism of edema formation, however, is somewhat more complex than a simple balance between the hydrostatic loss of fluid from the arteriolar end of the capillaries with failure of reabsorption at the venous end because of low colloid osmotic or oncotic pressure. In the first place, such a concept fails to take into account the lymphatics whose flow is greatly increased with any tendency toward accumulation of interstitial fluid and thus return this fluid to the blood stream.

In the second place, if all the fluid in the blood stream ran out into the interstitial spaces, there would not be enough to produce pitting edema since about ten to fifteen pounds of extra fluid must be accumulated in an average individual to produce pitting. Thus, any concept of edema formation must include some mechanism for retention of extra salt and water by the kidneys. Borst⁵¹ and Peters⁵² proposed that when blood volume is low, the kidneys retain more salt and water in an effort to maintain homeostasis, or normal blood volume. Borst found that transfusion in a patient with nephrotic edema with rise in venous pressure effected an increase of thirty times the control level of salt and water excretion by the kidneys. Squire⁵³ found a 20 to 30 per cent reduction in blood volume and demonstrated a fall in hematocrit from hemodilution just before the onset of spontaneous diuresis. In some nephrotic patients with anemia, the plasma volume is normal as compared to the accepted normal value, but anemic patients usually have an increase in blood volume⁵⁴ so that, comparatively speaking, even these patients have a low blood volume. Plasma volume varies reciprocally with edema formation.^{55,56} Thus, it appears that plasma volume reduction could be the trigger mechanism for retention of salt and water by the kidney. Such retention could result from a reduced filtration rate with normal tubular reabsorption, or from increased tubular reabsorption alone, or from both. Renal blood flow and filtration rate may be normal⁵⁷⁻⁵⁹ or even increased⁶⁰ in edematous nephrotic subjects, so that increased tubular reabsorption must be the primary factor. Antidiuretic substances have been reported⁶¹ in nephrosis, but these do not account for the sodium retention which must accompany water retention, or else the blood sodium level would be reduced in nephrosis. Recently, Luetscher⁶² demonstrated a new potent sodium-retaining adrenal cortical hormone, aldosterone, in unusually large quantities in patients with nephrotic, cardiac, and hepatic edema. Administration of this hormone to nonedematous subjects produces edema.^{63,64} He has now isolated this in crystalline form from the urine of nephrotic subjects.⁶⁵ The fact that edema may not be present in patients with primary aldosteronism (adrenal cortical tumors with high assays for aldosterone in both tumor and urine) poses something of a problem, but as Luetscher points out,⁶⁶ adrenal tumors may have mixtures of hormones, and whether or not edema occurs may depend upon the proper concentration of the various secretions. Barring a few details such as the above, the problem of edema in nephrosis seems to be well on the way to a final solution. Simultaneous stimulation of ADH production by the low blood volume in nephrosis might account for the difference.

Thyroid function in nephrosis has been a subject of debate. Recant and Riggs found the basal metabolic rate to be low even after correction for edema,⁶⁷ but the I_{131} uptake was normal or high and the blood protein-bound iodine rose in response to thyrotropic hormone administration. They believe that the low PBI found by Peters and Man⁶⁸ is caused by the hypoproteinemia.

CLINICAL PICTURE

The most striking feature of nephrosis is the edema which is a soft pitting edema in contradistinction to the harder edema of congestive heart failure, which is associated with a sort of toughness of the skin. Since the patient is not orthopneic, the edema is more likely to accumulate where the tissue pressure is low, most frequently around the eyes. Edema may be preceded by a period of malaise, anorexia, nausea, diarrhea, and irritability. Albuminuria may be discovered by chance examination of the urine or because of recognition of the edema. I have seen two cases of edema preceding the appearance of albuminuria by forty-eight hours. This has also been reported by Rapaport and Kohn.⁶⁹ Newman reports a case of so-called "elementary nephrosis" in which there was edema which responded to ACTH therapy, slightly low PAH and inulin clearances with a normal filtration fraction, normal blood chemistries including blood cholesterol and serum proteins, and no albumin in the urine after the first examination, despite continuing edema.⁷⁰ Edema may disappear permanently after a few days or may come and go for years. Free intervals up to nine years with recurrences have been recorded, though recurrences after six months are uncommon and they are rare after eighteen months with a negative urine. In some patients the urine and edema never clear and they go progressively to renal failure. Ascites and hydrothorax are seen frequently, and interlobar effusions are sometimes mistaken for tumors of the lung. Pulmonary edema and retinal edema are rare. Edema may appear with infections, physical stress and strain, or for no apparent reason. Certain viral infections, notably hepatitis⁷¹ and measles^{72,73} may induce diuresis, though I have seen an exacerbation with measles. The fluid has an opalescent milky character and has a protein content of less than 0.1 per cent.⁷⁴ Edema is present regularly with the serum total protein less than 4 Gm. per 100 c.c.⁷⁵ and is usually found if the serum albumin is less than 2.5 Gm. Eventually, complete recovery occurs or the patient dies with renal failure or with an intercurrent infection. The blood pressure may rise moderately and transient renal failure may be found with exacerbations.

Infections of various types are common, especially pneumococcal infections, and particularly pneumococcal peritonitis. These have been attributed to the low serum gamma globulin. Malaise, anorexia, diarrhea, nausea, and vomiting may be present. Most patients are undernourished.

URINE

The volume varies with edema formation and diuresis, and the specific gravity may be high. ¹

Proteinuria.—Proteinuria varies widely from a trace to as much as 110 Gm. daily in one case reported.⁷⁶ The average when edema is present is about 10 Gm. a day.

Glycosuria.—Glycosuria may occur and is renal in origin.

Microscopic Examination.—Erythrocytes are often present, especially in subacute glomerulonephritis and the urine may be grossly bloody. In so-called "pure nephrosis" they are less common, although they have been seen in proved cases. Leukocytes are often present, even without demonstrable infection.

Doubly refractile material forms a maltese cross when viewed through a polarizing microscope or when the light comes through two polaroid discs so rotated that a minimum of light passes through. It is interesting that lipemia without renal disease does not produce lipiduria.¹³

Hyaline, granular, and fatty cases are often visualized.

BLOOD

The plasma proteins are low primarily because of loss of albumin through the kidney and, secondarily, because of anorexia and low protein intake.⁷⁷ The total protein may be as little as 3 Gm. per 100 c.c., and the albumin may be below 1 Gm.⁷⁷ Fibrinogen is markedly increased from a normal of 0.3 to 1.19 Gm., and this probably partially accounts for the high sedimentation rate. Block⁷⁸ found the latter more closely related to the depressed serum albumin. Globulin is usually increased slightly and may be as high as 10.7 Gm. per 100 c.c.⁷⁹ Alpha and beta globulins are increased while gamma globulin is decreased.^{40,41} S-70, 40-70, and alpha-2 and beta lipoprotein blood levels are elevated.⁸⁰

The antistreptolysin-0 titer is low but has been found to be low before the renal lesion existed and therefore, despite the high urine level, is not due to loss in the urine.⁸¹ Serum complement is depressed.⁸²

Lipemia and hypercholesterolemia are constant except in emaciated patients. Fishberg reports blood cholesterol levels up to 2,300 mg. per 100 c.c. and levels up to 2,000 are not rare.¹³ Extensive atheromatosis may be found even in young children.⁸³

The serum electrolytes are usually normal though the blood sodium has been found low.⁸⁴ This may be artifactual, however, since the high blood lipid content depresses the total serum water in which sodium is dissolved, giving an apparent low sodium value for the amount of serum measured. I have seen one patient who has had three attacks of shock brought on by massive sodium loss in the urine. Each time, the urine sodium returned to normal after ACTH therapy. Blood potassium, $\text{PO}_4 \equiv$, and SO_4^{--} are normal. Serum calcium may fall to as little as 3.5 mg. per cent⁸⁵ because of the hypoalbuminemia since a large part of the calcium is bound to albumin. Ionized calcium (which is unbound) is normal. Calcium is also lost in the stool.⁸⁶

Anemia is not unusual and is hypochromic. Luetscher⁹⁰ mentions that eosinophilia is not unusual.

RENAL FUNCTION

PSP, specific gravity of urine, renal blood flow, and glomerular filtration rate are usually normal and may even be supernormal (see above). In severe exacerbations, all functions may be depressed transiently or may not return to normal at all.

PROGNOSIS

Prognosis in nephrosis has been very vague until recently. Epstein thought that it was a benign disease.⁴² Holt and Howland⁸⁷ lost only two of twenty patients and they died of infection. Schwarz and Kohn⁸⁸ had five of nine die, and of forty followed for twenty years, twenty-two died. Block and collaborators⁷⁸ followed forty children for fifteen years: twenty-six were alive, twenty-two of these well for three months to sixteen years, four still had symptoms, and ten died. Loss of probably four more might be anticipated, giving a probable mortality rate of 50 per cent. The best figures have been gathered by Conrad Riley from 500 patients reported by different investigators at the 1954 Conference on the Nephrotic Syndrome.⁸⁹ At that time, there was a two-year mortality rate of about 30 per cent, a three-year mortality rate of about 38 per cent, and a four-year mortality rate of 40 per cent in patients who received no steroids. The figures were about the same in those who were treated for edema only. The mortality rate was statistically significantly less among those treated according to a planned schedule, the thirty-three-month mortality rate being about 20 per cent, which was the longest follow-up in that group. However, the groups were rather small at the end of the study since, in the life table technique, patients with whom contact is lost are dropped out of the study. At the beginning there were 164, 102, and 171 cases in each respective group, and at the end 62, 21, and 23. Despite statistical significance, judgment must be withheld as to the effect of steroids.

The cause of death used to be chiefly intercurrent infections, especially pneumococcal ones, but since the advent of antibiotic therapy the causes of death are: (1) renal failure, (2) heart failure, (3) edema of the lungs and brain, (4) thrombosis of the aorta or pulmonary artery, and (5) venous thrombosis.⁹⁰

The mortality rate in children seems to be lower than that in adults but, unless a needle biopsy or autopsy is done, it is not possible to be even reasonably sure as to with what disease one is dealing. Response to treatment in adults is said by some^{91,92} to be as good as that of children. Significant statistics as to mortality rate with treatment are not available.

Relapse is rare after one and one-half years of complete freedom from albuminuria, but has been reported after five and seven years.⁹³

Some patients who have a cessation of the activity of the disease after a significant amount of renal damage has occurred grow physically until the growth spurt of puberty usually proves too much for them.⁹⁴

TREATMENT

Diet.—Epstein⁴² originated the high-protein diet in nephrosis to raise the BMR through the specific dynamic action of protein and thought that edema was eliminated through stimulation of the thyroid gland. Addis⁹⁵ found that a high-protein diet accelerated the onset of renal failure in rats with damaged kidneys and, therefore, opposed the use of a high-protein diet in active glomerulonephritis and in nephrosis, irrespective of the state of renal function. This

stand has found little support in recent years. Evidence is good that a high-protein diet promotes regeneration of the serum proteins (see "Pathogenesis of Hypoproteinemia" above) and that a low-protein diet interferes with regeneration.

Blainey⁹⁶ found a straight-line relationship between protein intake and positivity of balance even up to 200 Gm. per day. One girl gained 488 Gm. of nitrogen or 6.6 pounds of protein in 99 days. Each gram of nitrogen was associated with three times its weight in water. She started with approximately a 20 per cent deficit in protein. Intracellular substance is one-third protein and two-thirds water, so most of her gain was in the cell.³⁶

Squire³⁶ believes that the nephrotic patient needs more than the normal requirement plus albumin loss because serum protein composition is highly specialized and 100 per cent utilization of amino acids is not to be expected. Grabfield and Prescott⁹⁷ and Kelly⁹⁸ say that these patients have a high sulfur requirement.

Farr⁹⁹ thinks that a normal protein intake is sufficient. He found that the N.P.N. loss in the urine increased rapidly with diets of 0.6 to 0.8 Gm. of nitrogen per kilogram. However, four of his patients were edema free so their serum proteins may not have been as low as those of Blainey. Farr used meat supplements; Blainey used a salt-free milk powder. Farr's patients had a steady caloric intake while Blainey's did not. All in all, the best diet seems to contain about 120 Gm. of protein and about 2,800 calories. Nitrogen retention, if present, contraindicates a high-protein diet.

If edema is present, a low-sodium diet is indicated, but this may have to be compromised in order to appeal to the patient's appetite. A low-fat diet has no effect on the lipemia.

Bed Rest.—Bed rest is indicated with massive edema and even with albuminuria, provided the latter can be eliminated in a reasonable period of time. If not, the patient should be allowed up after about two months. Bed rest almost always promotes a considerable amount of diuresis.

Raising Osmotic Pressure.—Raising osmotic pressure does produce a diuresis in about half the patients, but there is no real permanent benefit. Acacia,¹⁰⁰ 1 Gm. per kilogram in 30 per cent solution, is effective but becomes deposited in the liver cells in large quantities and produces chronic hypoproteinemia.¹⁰¹ Salt-free concentrated albumin 50 Gm. per day helps temporarily in half the patients. Dextran is about the same, but all of these measures are temporary and have no effect upon the albuminuria. These substances may help induce diuresis in patients resistant to steroids.

Thyroid.—Thyroid is of no proved value.

Diuretics.—Diuretics are of little real help, nor are *Cation Exchange Resins*.

Clearing Up of Infectious Foci.—This should be decided upon without regard for the nephrosis, except to attempt to control the infection with antibiotics before surgery, if possible.

Antisymphilitic Therapy.—Antisymphilitic therapy is promptly successful in syphilitic cases, but they usually clear spontaneously in a short time, regardless.

Measles.—Induction of measles produces a remission in less than half the cases,^{72,73} so-called nephrotic syndrome of glomerulonephritis responding less well. The author has seen one patient who had a relapse with the onset of measles. Fishberg also mentions this.¹³ Since results are not as good as with steroids, this has been abandoned.

Nitrogen Mustards.—Nitrogen mustards¹⁰² induce a diuresis in about one-third of the patients, but the treatment is unpleasant and is inferior to steroids.

Malarial Therapy.—Malarial therapy is used chiefly in England and produces remission in many cases for three to six months, but is still less effective and desirable than hormone therapy.

STEROID OR HORMONE THERAPY

Treatment with ACTH, cortisone, prednisone, and allied steroids is by far the most satisfactory method devised up to this time. It was first reported by Farnsworth¹⁰³ and her report was followed by reports from Riley,¹⁰⁴ Metcoff,¹⁰⁶ and Rapaport.¹⁰⁷ All investigators at first used short courses of six to ten days, employed rather small doses, and merely attempted to eliminate edema. Diuresis usually followed withdrawal of the medication, whereas up to about the eighth day albuminuria and weight increased. With somewhat longer courses, diuresis was found to begin even while the patient was still receiving hormones. As high as 90 per cent of patients had diuresis.

Lange,¹⁰⁸ in 1950, then devised a treatment with 400 mg. of cortisone or 100 mg. of ACTH Gel on three consecutive days each week, to be continued for a year or even more if relapse occurs. The intermittency has the advantage of reducing, though not completely eliminating toxic reactions and the prolongation of treatment maintains patients more frequently free of edema and albuminuria than short courses do. He has had only one death in twenty-four patients (nineteen children and five adults) with an average follow-up of three years. Sixty-one per cent are proteinuria free and thirty-nine per cent have varying degrees of proteinuria.

I started, in 1951,¹⁰⁹ a series of patients experimentally on continuous daily treatment with corticotropin Gel starting with 1 mg. per pound net weight and increasing to as much as 2 mg. per pound if no improvement occurred within ten days to two weeks. Achievement of a protein-free urine was the aim from the beginning of this method to see if it would prevent the renal failure which can progress despite lack of edema as long as proteinuria is present. Dosage was therefore readjusted until this was accomplished or until a dose of 2 mg. per pound was reached. When albumin was reduced to a trace or negative, which required an average of one to three weeks, dosage was continued for two weeks more, then abruptly reduced to the same dose every other day. Dosage was then slowly reduced each time over a period of about four months. If relapse occurred or in the presence of infection, the dose was doubled and then dropped rapidly to just above the previous amount. In the past five years, no patients have died, though one has failed to respond in any way to the treatment. All except this patient have been free of edema at one time or another, with the exception of the edema of Cushing's disease, but proteinuria relapses have been

common, though usually easily controlled by increased dosage. Of twenty-five patients followed three to five years, thirteen have been completely well for six months or more and eleven others are still under active treatment. One did not respond at all. Growth and development have been grossly normal, though one little girl developed precocious puberty and was changed to Lange's technique because of this and osteoporosis of the spine with a collapsed vertebra. She was very resistant and had been on 2 mg. per pound for almost a year. Since routine use of antibiotics along with steroids seemed to encourage invasion of the blood stream by unusual and resistant bacteria, antibiotics were not employed routinely, but the patient was checked daily for infection. A 200 mg. sodium diet was employed and potassium salts, about 4.5 Gm. per day, were given.

Most investigators now have a protein-free urine as their goal¹¹⁰ and are using larger doses and longer periods of treatment. Patients seem to be free of albumin for a greater percentage of time than with older techniques and can live a more normal life. Short-course therapy has no mortality advantage over no treatment and may be worse.¹¹¹ My patients are permitted to take moderate exercise after the urine has been clear for two weeks.

At present, the following plan of treatment with steroids seems reasonable. A ten-day course of about 1 mg. per pound of ACTH Gel or prednisone, or 4 mg. of cortisone per pound wet weight with a two-day taper-off is tried. If diuresis occurs and the urine is free of protein or has no more than a trace for three to four weeks or longer, a second course may be tried. If the patient relapses a second time, it is usually desirable to use some sort of prolonged treatment. If there is no response, or an incomplete response to the short course, then treatment is prolonged until diuresis occurs and until albuminuria is reduced to a trace or negative. If there is absolutely no reduction in albuminuria after two weeks, the dose is raised to $1\frac{1}{2}$ mg. per pound, and if still no response in three weeks, the dose is increased to 2 mg. per pound. If this fails after two more weeks, treatment may be discontinued for a month or two and tried again, or else Lange's technique of three consecutive days a week can be started immediately. This will sometimes produce a diuresis when continuous treatment cannot and the reverse is also true. After the urine is free of albumin or has contained only a trace for about two weeks, a two-day taper-off is given and the patient is started on Lange's technique since this is safer and produces fewer reactions to the steroids. The dosage for his plan seems a little rigid without regard for the weight of the patient. Two milligrams of ACTH Gel or prednisone per pound wet weight with a maximum of 100 to 150 mg. seems about right. If this fails to control the albuminuria, then one can use the longer acting ACTH Zinc for three days a week or ACTH Gel for four days a week. An alternate method when relapse and 1- to 4-plus albuminuria reappear is to give a two- to four-week course of daily treatment until this clears, then resume the interrupted technique of Lange.

The question of when to stop is still a moot question. Rapaport's¹¹² suggestion that it be continued until the urine has been albumin free for four weeks may prove to be practical, but there has been no report of his results or how frequent relapses have been. If the latter are frequent, then it is better to carry

out treatment over a longer period of time since relapses interrupt school and activities and are frustrating and discouraging to the parents. On the other hand, a year's treatment regardless of results, as advocated by Lange, is probably unnecessary in around 15 per cent of patients. Our original period of continuous daily treatment usually lasted about four months if there were no relapses. The patients were free of edema and albuminuria for about three and one-half months. Time will probably settle the question of when to stop treatment.

The patient's family should be taught to check the urine for albumin and should do so every morning for a year after treatment is discontinued. Prompt resumption of treatment if albuminuria becomes 2 plus or more makes control easier.

An aggressive, optimistic attitude in the treatment of nephrosis will yield better control than was once thought possible and, whether we are prolonging life or reducing mortality rate or not, most patients are able to live a more normal and satisfactory life. It does seem, as of now, that we are keeping them from dying in renal failure crises, but there is no evidence that the underlying tendency is modified. This has to be overcome spontaneously.

PRECAUTIONS

Luetscher finds the blood sodium low in some patients with nephrosis and believes it may be caused by low-salt diets, antidiuretic hormone, or renal failure.¹¹³ He advises giving concentrated albumin which he found would raise the blood sodium by diuresis since hypertonic saline does not seem to help. Reduction in water intake may produce severe oliguria and hyperkalemia, especially if ACTH is given. If steroids are administered when the blood sodium is low and while at the same time salt is restricted below 5 Gm., water intoxication may occur with headache, nausea and vomiting, mental confusion, muscular hyperirritability, convulsions, hypertension, pulmonary edema, oliguria, and azotemia. Therefore, it is important to raise the blood sodium with albumin before proceeding.

Since potassium is released by ACTH, a good urine flow must be promoted to prevent potassium intoxication. As diuresis sets in, potassium deficiency may require that potassium be given. Even paralysis has been observed in this situation and 6 Gm. or 90 meq. daily may be necessary to overcome the deficit.

The most serious reaction to treatment which we have encountered in long-term daily therapy is osteoporosis and vertebral collapse. This has not been reported with Lange's schedule. Patients are watched carefully for infection but are not given therapeutic doses of antibiotics, only 0.5 Gm. of sulfa drug daily. There has been no serious trouble with infection. Two patients have had convulsions and these were easily controlled and prevented with Dilantin Sodium. Moonface is present in practically all patients while on larger doses even with Lange's schedule. Every patient must have a chest x-ray and, if extensive arrested tuberculosis is present, antituberculous therapy should be given simultaneously. If blood pressure and N.P.N. rise rapidly treatment will usually have to be discontinued.

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Book Reviews

CLINICAL RECOGNITION AND MANAGEMENT OF DISTURBANCES OF BODY FLUIDS. By John H. Bland, M.D., ed. 2, Philadelphia, 1956, W. B. Saunders Company, 522 pages. Price \$11.50.

This book by one of the authorities in the field of water and electrolytes is divided usefully into chapters so that material may be easily found. It is well organized, accurate, and easy to read. It is far more complete in detail than most books of this type. I should recommend it for every physician and student of medicine, including both internists and surgeons.

A. J. M.

DIAGNOSIS AND TREATMENT OF PERIPHERAL VASCULAR DISORDERS. By David I. Abramson, New York City, 1956, Paul B. Hoeber, Inc., 30 chapters, 537 pages, 82 figures, 18 tables.

This excellent book is divided into three sections. The first is devoted to discussions of symptoms and signs of vascular abnormalities in the extremities. Specific disorders of the arterial, venous, and lymphatic systems are taken up in the second section. The last section deals with the anatomic, physiologic, and pharmacologic facts which are necessary for the understanding and sensible treatment of vascular disease.

Differential diagnosis is stressed throughout the text and special attention is given to the evaluation of symptoms when vascular and nonvascular diseases coexist in the same part. Prognosis receives its proper emphasis and the medical rather than the surgical approach to therapy is given prominence in most chapters. Comprehensive tables, the liberal use of heavy type and italics, and a good index add to the usefulness of the book as a ready source of reference.

This book covers the field of peripheral vascular disease in a comprehensive and authoritative manner. Although intended for the busy family physician, this volume should be of interest to the vascular consultant as well as other physicians who deal with peripheral vascular disease.

J. W. E.

ATLAS UND KURZGEFASSTES LEHRBUCH DER PHONOKARDIOGRAPHIE UND VERWANDTER UNTERSUCHUNGSMETHODEN. By Priv.-Doz. Dr. Med. K. Holldack and Dr. Med. D. Wolf, Stuttgart, Georg Thieme Verlag, 171 pages, 175 illustrations. Price D.M. 49. 50.

This work is intended to serve as an introduction to phonocardiography and related fields. It is presented in the form of an atlas of the phonocardiographic findings of the more common disorders of the heart and included tracings from the carotid artery, jugular vein, respiration, and esophageal pulse. The illustrations are technically excellent reproductions of tracings obtained partly by a multichannel photographic phonocardiograph and partly by a multichannel direct-writer. Selective sound filters were used and the sound tracings were simultaneously obtained for five different frequency ranges. The illustrations are supplied with detailed descriptive legends. It would have been helpful if the different acoustic events had been indicated by symbols directly on the tracings instead of being referred to only in the text. The connecting text, which was short by necessity, still contains a good deal of information and is clinically oriented.

The work starts out with a short introduction into the physical principals, apparatus, and technique of phonocardiography and its related fields. After a presentation of the different acoustic elements of the normal and abnormal heartbeat, it takes up the phonocardiographic findings in the different clinical disorders. About one third of the whole book is devoted to congenital heart diseases. The references are alphabetically arranged and include German, French, British, and American publications. This treatise is a fairly comprehensive review of phonocardiography and could be read with profit by those familiar with German medical writings.

E. R.

Announcements

INTERNATIONAL CONGRESS ON THE CIRCULATION

THE TERCENTENARY OF THE DEATH OF WILLIAM HARVEY (1578-1657) will be commemorated by an INTERNATIONAL CONGRESS ON THE CIRCULATION. The main theme will be: "A REVIEW OF THE PRESENT KNOWLEDGE OF THE CIRCULATION."

Monday, June 3: Chairman: The President.

10 A.M. Opening of the Congress.

"Knowledge of the Circulation From the Seventeenth to Twentieth Centuries." Professor K. J. Franklin, Medical College, St. Bartholomew's Hospital, London, Dr. F. A. Willius, Mayo Clinic, and Dr. J. Fulton, Yale University.

2 P.M. Chairman: Professor G. W. Pickering, Oxford.

"The Role of the Heart in the Circulation." Dr. L. Katz, Chicago, Dr. P. Wood, National Heart Hospital, London, Professor K. Matthes, Heidelberg, and Dr. Silvio Weidmann, Berne.

Tuesday, June 4: Chairman: Sir Clement Price-Thomas, Westminster Hospital, London.

9:30 A.M. "The Results of Cardiac Surgery." Sir Russell Brock, Guy's Hospital, London, Professor G. d'Allaines, Paris, Professor C. Crafoord, Stockholm, and Dr. M. Campbell, Guy's Hospital, London.

2 P.M. Chairman: Dr. C. S. Beck, Cleveland.

"The Coronary Circulation." Dr. D. E. Gregg, Washington.

Wednesday, June 5: Chairman: Professor J. McMichael, Postgraduate Medical School, London.

9:30 A.M. "The Pulmonary Circulation." Dr. A. Cournand, New York, Professor C. V. Harrison, Postgraduate Medical School, London, and Professor S. Radner, Lund, Sweden.

2 P.M. "The Foetal Circulation." Dr. G. S. Dawes, Nuffield Institute for Medical Research, Oxford.

Thursday, June 6: Chairman: Dr. M. Critchley, King's College Hospital, London.

9:30 A.M. "The Cerebral Circulation." Dr. S. Kety, National Institute of Health, Bethesda, Professor Th. Alajouanine, Paris, and Dr. E. H. Botterell, Toronto.

2 P.M. Chairman: Professor Sir James Learmonth, Edinburgh.

"The Splanchnic Circulation." Dr. S. Bradley, New York, Dr. S. Sherlock, Postgraduate Medical School, London, and Professor R. Milnes Walker, Bristol.

Friday, June 7: Chairman: Professor A. Kekwick, Middlesex Hospital, London.

9:30 A.M. "The Peripheral Circulation."

"Circulation Through the Limbs." Professor H. Barcroft, St. Thomas' Hospital, London.

"Vascular Innervation." Professor W. D. M. Paton, Royal College of Surgeons, London.

"Pathology of Vessels." Professor J. H. Dible, Postgraduate Medical School, London.

"Surgery of Occlusive Arterial Disease." Professor C. Rob, St. Mary's Hospital, London.

The Congress will be followed by a week-end Conference on the more personal and biographical aspects of William Harvey's life at his birthplace, Folkestone, Kent.

Saturday, June 8: Chairman: Sir Geoffrey Keynes.

10:30 A.M. Harvey's birthplace: Professor T. Hare, London.

Harvey at Cambridge: Professor Sir Lionel Whitby, Cambridge.

Harvey at Padua: Professor A. P. Cawadias, London, and Dr. L. Chauvois, Paris.

Afternoon: Visit to Canterbury Cathedral.

Evening: Civic Reception.

CARDIAC ARRHYTHMIAS will be the subject of a two-day Postgraduate Course on The Heart, to be presented on February 25 and 26, 1957, at the UNIVERSITY OF KANSAS MEDICAL CENTER, Kansas City, Kansas. The program is designed specifically to aid the doctor in general practice in the treatment of these frequently encountered anomalies. Much of the teaching will be accomplished through demonstration of cases presenting arrhythmias.

The guest faculty includes: Dr. Samuel Bellet, University of Pennsylvania; Dr. Herman K. Hellerstein, Western Reserve University; Dr. Calvin F. Kay, University of Pennsylvania; and Dr. R. Bruce Logue, Emory University.

Registration fee for the course is \$30.00. Additional information about the program or registration card will be sent upon request by writing to the Department of Postgraduate Medical Education, University of Kansas School of Medicine, Kansas City 12, Kansas.

THE UNIVERSITY OF MINNESOTA announces a continuation course in RECENT ADVANCES IN INTERNAL MEDICINE FOR INTERNISTS to be held at the Center for Continuation Study on the University Campus March 4 to 6, 1957. As in previous years, fundamental advances related to clinical practice will be stressed. Areas to be covered this year include infectious diseases, neurology, cardiology, and gastroenterology.

Guest speakers will be Dr. Max B. Lurie, Professor of Experimental Pathology, Henry Phipps Institute, Philadelphia, Pennsylvania, and Dr. Carleton B. Chapman, Professor of Medicine, Southwestern Medical School, Dallas, Texas. Remainder of the faculty will include members of the faculties of the University of Minnesota Medical School and of the Mayo Foundation. The course will be presented under the direction of Dr. Wesley W. Spink, Professor, Department of Medicine.